

DISORDERS OF METABOLISM

An Account of Five Cases.

Presented for

The Wightman Prize in Clinical Medicine

by

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INTRODUCTION

The cases for this essay have been chosen to illustrate conditions in which medical research is now particularly interested. They are all cases to which, in the early stages, successful treatment can be rapidly and effectively applied. This treatment which consists essentially of endocrine substitution therapy alleviates the clinical features although it does not cure the disease. The advances which have led to the use of this therapy have been too recent to allow the prognosis of conditions treated in this way to be known exactly, or the ultimate progress of pathological complications in these diseases to be understood fully.

In the cases described the signs and symptoms caused by the original disease are made more complex by the presence of clinical features produced by a condition which is commonly supposed to complicate the initial disease. In the discussions of the cases the treatment is considered in relation to its influence on the production of these complications; an attempt is made to determine the reason why such complications occur and their relation to the initial disease. It is only by such a study that rational and effective prophylactic therapy can be applied in the future.

Medical teaching in Edinburgh stresses the value of accurate diagnosis and rational therapy but it does not stress to the same extent the fact that a careful clinical study of the patient may bring to light facts which if applied in clinical research may result in advances in medical knowledge. These cases have presented complicated clinical problems; it has been the object in the discussions to try to elucidate these problems. When this has successfully been done the ultimate prognosis for patients who suffer from metabolic diseases which previously were fatal in the acute stages, will be improved because the complications now associated

associated with the late stages of the disease will be understood and subject to therapeutic control.

The hospital and ward in which the patients were treated is stated at the beginning of each case, as also is the name of the physician who had charge of the case. Grateful acknowledgement is made to these physicians for permission to report on, and discuss the cases under their charge.

C. W. M. Wilson,

May 1949.

CASE I.

PROFESSOR D. M. DUNLOP.

MR. RYSZARD RAGINIA

Ward 21,

Royal Infirmary

of Edinburgh.

DIAGNOSIS: MALABSORPTION SYNDROME.

Mr. RYSZARD RAGINIA

aet. 20 Single

Crossrigg,

Hutton,

Berwick - on - Tweed.

Occupation: Factory Worker.

Doctor: Dr. Hair

Chirnside,

Berwick - on - Tweed.

Date of Admission: 1. 12. 48

Date of Examination: 9. 12. 48

Date of Discharge: 4. 2. 49

Complaint: Tiredness, loss of energy and diarrhea for
three weeks, pallor and palpitations for
one week.

HISTORY

History of Present Illness

The patient is of Polish nationality and lived in Poland until he was twelve years old when his family was broken up and he was removed by the Russians. He was sent to Siberia where he was treated as a prisoner and made to work on a Government Collective Farm. He was housed in the farm buildings along with a number of other Russian Prisoners. Every day he had to get up early in the morning and go out into the fields where he did heavy farm labour. The working hours were long and no holidays were allowed. The patient's diet was very poor and consisted of:

Fresh corn plucked from grain fields as
he passed through them.

Vegetables and vegetable soup. Often the
vegetables were raw.

Meat was never obtained and fish was only
occasionally allowed. The patient never had any milk.

After a year and a half the patient began to feel very tired and the walk to his work and the work itself became very arduous and difficult. The patient's appetite began to disappear and for two or three weeks he lost all desire for food of any kind; at the same time his stool became liquid and of a very pale yellow colour and developed an offensive odour. The patient suffered from no pain, visual disturbances or itching. These symptoms remained and increased in intensity until finally the patient went to see the camp doctor who told the patient there was nothing wrong with him and that he must continue to work. At this time the patient was passing four or more stools per day.

The symptoms remained essentially the same for six months and the patient's appetite remained poor though he did eat some of the food given to him. At the end of two years in Siberia the patient was transferred to South Russia where a camp had been formed to recruit and train a Polish Army under British control. Here, for the first time, the patient received treatment for his condition. He was treated by the camp doctor with liver injections and iron; he received twenty-five injections of liver extract, one injection being given each day, and three tablets containing iron daily. The patient could get as much food as he wished and there was no limit to the quantity of meat or vegetables which he could eat. The doctor told him to eat as much ^{meat} as he could, vegetables and mashed fruit; he was also told to drink large quantities of milk, and a glass of port wine each day. Under this treatment his symptoms gradually improved and after three months his diarrrhea, tiredness and appetite had completely disappeared.

He remained in South Russia for ten months: during the seventh month as a result of eating some fresh fruit the patient contracted dysentery with severe abdominal pain, loss of weight, the passage of frequent stools of a consistency like

like red jelly, "the loss of large quantities of blood", and complete loss of appetite. The patient was treated by the camp doctor with carbon and opium by mouth. For about three weeks he ate a few biscuits only and drank strong coffee and wine each day. The disease had disappeared a month after the appearance of the first symptoms.

The patient next moved into Persia and was stationed in a camp near Teheran. Here he contracted malaria and suffered from three attacks of it which were successfully treated with quinine. He also suffered from a short bout of food poisoning with vomiting and diarrhea with the passage of two or three semi-liquid brown stools each day. This was treated by carbon tablets and castor oil and within six days the patient had recovered.

After eight months in Persia the patient went on to India with his mother and father, and the family lived about 200 miles outside Bombay. While he lived in India the patient had a full diet and there was no difficulty in obtaining food. His diet consisted of:

Breakfast: 3 boiled eggs
2 pieces of bread and butter
Tea and milk
Pine apple.

Dinner: Plate of vegetable soup.
Meat, potato and vegetables
3 or 4 bananas

Tea: Bread and butter
Bacon
Tea or coffee

Supper: 2 cups of tea or coffee
3 eggs and bacon
2 pieces of bread and butter
Grape fruit.

He remained in India for about four years and nine months

months and during this period he had eight or nine attacks of malaria and had three recurrences of the symptoms which he had had in Siberia. Two of these attacks occurred while the patient was at home and he was treated in the local hospital and the third occurred while he was in the hills. During his sojourn in India the patient was constantly tired and was suffering from diarrhea with the passage of two or three pale offensive watery stools each day. He states that all the time while he was in India his red blood count averaged just over three million cells per cubic millimetre. When the diarrhea became worse and the patient became tired, with a marked loss of weight, breathlessness, palpitations and thumping in his blood-vessels and chest he used to go to hospital for treatment. At the beginning of the first attack the patient noticed some soreness of his mouth and tongue, but noticed no changes in his skin or visual disturbances. He was treated in hospital with liver injections, iron tablets, multi-vitamin tablets and Horlicks three times a day; he was discharged at the end of three months with some improvements in his symptoms although he states that his red blood cell count was only about three million. The next attack occurred while the patient was in the hills and he was treated by liver injections, injections of calcium lactate and strychnine.

The third attack occurred about four months before he left India and the symptoms were similar to those in the previous attacks, consisting of loss of weight, increased tiredness and diarrhea with some breathlessness, palpitations and thumping in his blood-vessels felt in all his limbs. There were no changes in the skin nor pain in the patient's mouth. Treatment was similar to that previously given in the Indian hospital and continued for four months at the end of which time the patient was still ill. However he obtained a passage to England at this time and accordingly set out and reached

reached Britain at the end of 1947. He was sent to the 5th General hospital, (Polish Resettlement Corps Hospital) East Evesleigh, in England, and there was treated for his condition which had markedly deteriorated during the voyage. On Admission he was suffering from diarrhea and loss of energy and was found to have a hypochromic anaemia and was diagnosed as suffering from sprue. He did not respond to fat-free diet, iron or liver extract treatment but folic acid treatment and concentrated vitamin therapy produced a very good result. He was discharged on 6.8.48 feeling much stronger, with stools of normal consistency and colour, and with a considerable gain in weight. His colour index was 1.0 and his red count 4 millions.

The patient then went to Berwickshire where he lives with his family, which has been re-united; he works in a paper factory. His diet now consists of:

Breakfast:	4 eggs
	2 pieces of bread and butter
	Tea with milk and sugar
Dinner:	A plate of soup
	Meat, potatoes and vegetables
	Pudding
Tea:	Bread and butter with jam or syrup
	Bacon
	Tea with milk and sugar
	Cheese
	Two eggs
	Tea or coffee.

About the 14th November 1948 the patient's stool became liquid, pale yellow in colour, and developed an offensive odour. He had to go to stool four or five times a day. He began to feel tired and very sleepy and unwell. He did not suffer from

from breathlessness, sore mouth or tongue or any abdominal symptoms. He states that there were no changes in his skin and that it did not feel itchy; he had no visual or eye symptoms. Shortly before admission to R. I. E. he became noticeably pale and began to feel his blood vessels thumping particularly in his upper arms, forearms, groins, knees, head and ears; he also suffered from palpitations. He saw his doctor on 29.11.48 who sent him to R. I. E. on 1.12.48. He was transferred to ward 21 on 7.12.48.

Previous History

The patient says he suffered from no illnesses while in Poland and never had scarlet fever or rheumatic fever or other illnesses of childhood. He has had no urinary troubles and is not liable to colds.

Family History

Mother and Father alive and well. They have had no chronic illnesses and are not troubled with diarrhea. The father is working on a farm and the mother is helping in the farmhouse. One brother aet. 14, and a sister aet. 16, alive and well. The other members of the family during their escape from Poland suffered some hardships, but probably none suffered as much as the patient.

Social History

The patient went to the Polish High School in India. He intends to continue his work in the paper mill in Britain. His father, mother, and brother live with him in a farm cottage of three rooms. He states that he does not smoke or drink although he has been smoking a few cigarettes while in the ward.

PHYSICAL EXAMINATION

General Inspection

The patient is a thin very pale boy, his pallor having a slight yellow tinge. He has a large broad, bossed forehead, pale lips and there is no colour at all in his cheeks. His

His hands are thin and dead white. There is marked wasting of his thenar and hypothenar muscles and the bones of his hands can almost be seen through them. The patient lies listless in bed and looks tired and sleepy. Although he is 20 years old he gives the impression of being a boy of 16 or 17 years.

Temperature: 98° F

Actual Weight: 6 stone 10½ lbs.

Ideal Weight: 10 stone 6 lbs.

Height: 5 feet 8 ins.

Alimentary System

Mouth: Clean and moist.

Tongue: It is slightly red at the tip and elsewhere is rather smooth. There is no indication of glossitis.

Teeth: Good. All present, no septic foci.

Tonsils: Normal and not inflamed.

Roof of mouth, tonsillar region and mucous membrane of lips: Pale. The throat is clear.

Abdomen

General Appearance: The abdomen is protruberant and distended, particularly below the umbilicus. The subcostal angle is narrow. The skin is soft, white and dry. The umbilicus and the hernial orifices are normal. The abdomen moves regularly on respiration.

Examination: No rigidity or tenderness. The entire abdomen is distended and resonant on percussion. The stomach as detected by percussion and auscultation is normal in size.

Liver, spleen, and kidneys impalpable. Ascending and descending colon palpable and distended with soft material.

Cardio Vascular System

Pulse

Rate: 82/min. Regular in rhythm and volume. The vessel wall is elastic and the vessel is small. The pulse

pulse volume is small.

Blood Pressure: 110/60.

Precordium

A long narrow chest. Pulsation marked in the 3rd. left inter-space and less obvious in the 4th. inter-space 3 inches from the mid-line.

No other pulsation: no dilated veins in chest or neck.

Apex beat: felt in 4th. left inter-space 3 inches from mid-line. Heaving expansion in 3rd. space above and internal to apex beat. Pulsation felt deep in supra-sternal notch.

The cardiac outline was determined by percussion:

on the left side the outer border is

3 inches from the mid-line in the 4th inter-space

2 " " " " " " " 3rd. " "

1½ " " " " " " " 2nd " "

on the right side the outer border is

½ an inch from the mid-line from the 2nd to the 4th ribs.

In the mitral area: the heart sounds are normal and regular but a fine faint systolic murmur follows the first sound. It is not propagated into the axilla but can be heard up the left side of the sternum as far as the pulmonary area. It is maximum in intensity in the 3rd inter-space.

In the aortic area: the heart sounds are fine, faint, and closed.

In the pulmonary area: the heart sounds are normal and regular and a fine systolic murmur can be heard.

In the tricuspid area: the heart sounds are normal and closed.

Respiratory System

The chest is long and thin and of the flat type. The suprasternal notch is low and the subcostal angle abnormally narrow. The costo-iliac space is less than one inch wide. The sterno-mastoid muscles are thin and small. The

The respiration is abdomino-thoracic . Respiration Rate:
20/minute.

Chest expansion normal and equal. No thrills or friction detected; vocal fremitus normal. The chest is resonant throughout and no abnormalities can be detected.

Central Nervous System

Mental State

The patient is intelligent and co-operative, but appears tired and listless.

Cranial Nerves

Nothing abnormal detected.

Motor Nerves: Sensory Nerves

Nothing abnormal detected. No signs of Tetany.

Reflexes

Accommodation and Pupil Reflexes normal.

Swallowing and palatal reflexes normal.

Abdominal reflexes present.

Upper limbs:

	Right	Left
Biceps	+	+
Brachio-Radialis	+	-
Triceps	+	+

Lower Limbs:

	Right	Left
Knee	-	-
Ankle	+	+
Plantar	?	flexor

All the muscles reflexes are weak and can be obtained only with difficulty.

Endocrine System

Thyroid normal. Sexual development normal. No glands detected in neck or axillae.

axillae.

Locomotor System

Joint movements free and unrestricted. Muscle power symmetrically equal, but the muscles are thin and in the limbs the bones can easily be felt through the muscles. Muscle tone is low. In the chest the ribs are protruberant and the costochondral junctions are prominent and easily felt. There is no Harrison's Sulcus. There is some bossing of the frontal bones in the forehead.

Blood Examination 8.12.48

H b. : 56%

Red blood cell count: 2.16 million per cubic m.m.

White Blood Cell count: 5,200 per cubic m.m.

Colour Index: 1.29

Reticulocytes: 1.8%

Mean Cell Volume: 115.7 c.μ

Packed Cell Volume: 25%

Blood film stained Leishman: Red blood cells show poikilocytosis, anisocytosis.

Skin.

The patient's skin is white, dry and rough. In the face it is soft and elastic but to the right of his mouth it is slightly rough and scaling over an area about a centimetre square. Over his hands it is rough, thick, white and scaling, particularly in the creases between his fingers and across the palmar creases. There is clubbing of all the terminal phalanges with antero-posterior curvature of the nails and fluctuation of the nail bases and tissue round the nail bases.

The skin of the feet is rough, dry and scaly and is particularly thickened over the heads of the metatarsals and heels. Scaling is present in the creases between the toes, and in the creases round the heels.

The skin of the back between the scapulae and over their

their lower angles is thick, rough and scaling.

Special Examinations

Examination of the Stools:

2.12.48 Stool - Pathological Examination.

The direct films showed a very few R.B.C. but no amoebae, cysts, ova or pus cells were seen and no organisms of the typhoid or dysentery groups were isolated on culture.

Personal Examination of Stool:

Macroscopic Examination: a copious, liquid, pale yellow stool with a most offensive smell. No solid matter could be seen in the stool.

Microscopic Examination: nothing abnormal detected. No ova or cysts seen, no fat or muscle fibres. Some vegetable fibres were seen.

Chemical Examination: The addition of iodine produced no colour in the stool. **Benzidine Test: Negative.**

Biochemical Examinations:

8.12.48 Plasma Proteins:

albumen: 2.46 gm %

globulin: 2.10 gm %

Serum Calcium: 8.0 mgm. %

Serum Phosphorus: 3.3 mgm %

Alkaline Phosphatase: 15 units

Non Protein Nitrogen: 27 mgm%

Marrow film: Megaloblastic.

24.12.48 Plasma Proteins:

Albumen: 3.36 gm %

globulin: 1.95 gm %

Serum Calcium: 8.0 mgm %

Serum Phosphorus: 4.3 mgm %

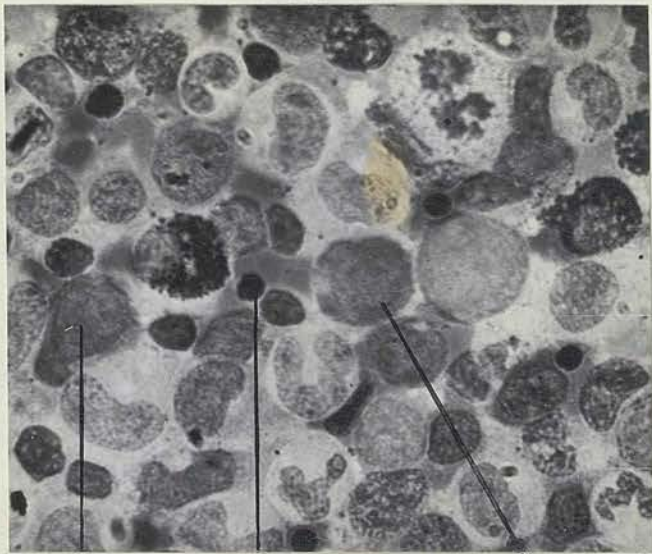
Alkaline Phosphatase: 9 units

Non Protein Nitrogen: 26 mgm %

10.1.48 Plasma Proteins:

STERNAL MARROW SMEAR

9:12:48



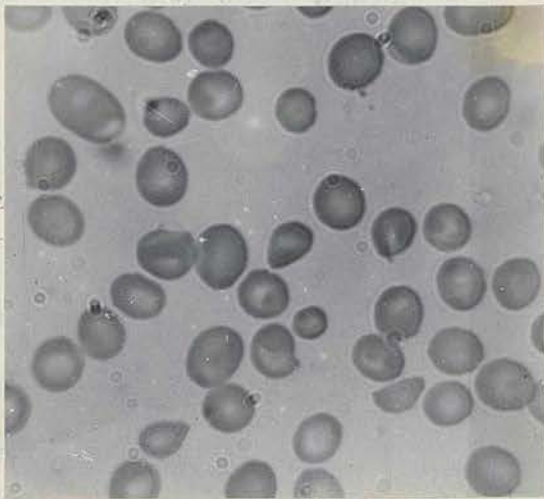
Megaloblast

Normoblast

Megaloblast

BLOOD FILM

6:12:48



Showing Macrocytosis, Anisocytosis, Poikilocytosis

10.1.48

Plasma Proteins:

Albumen: 3.31 gm %

globulin : 2.65 gm %

Serum Calcium: 8.7 mgm %

Serum Phosphorus: 5.0 mgm %

Alkaline Phosphatase: 10 units

Non Protein Nitrogen: 26 mgm %

Examination of the Bone Marrow:

Sternal Punctures were performed during the course of treatment and the smears were personally examined:

9.12.48 Numerous red blood cell precursors were present throughout the smear. Early megaloblasts, normoblasts, and the various stages of maturation between these cells with different degrees of haemoglobin in the cytoplasm were seen. In the majority of the megaloblasts the cytoplasm was of an inky-blue colour and no haemoglobin was visible in the cytoplasm at all. Relatively few normoblasts could be seen and the erythrocytes were not numerous. Normal white blood cell precursors were present.

22.12.48 } On each of these occasions the smears obtained
30.12.48 } were essentially similar to that examined
6.1.48 } on 9.12.48

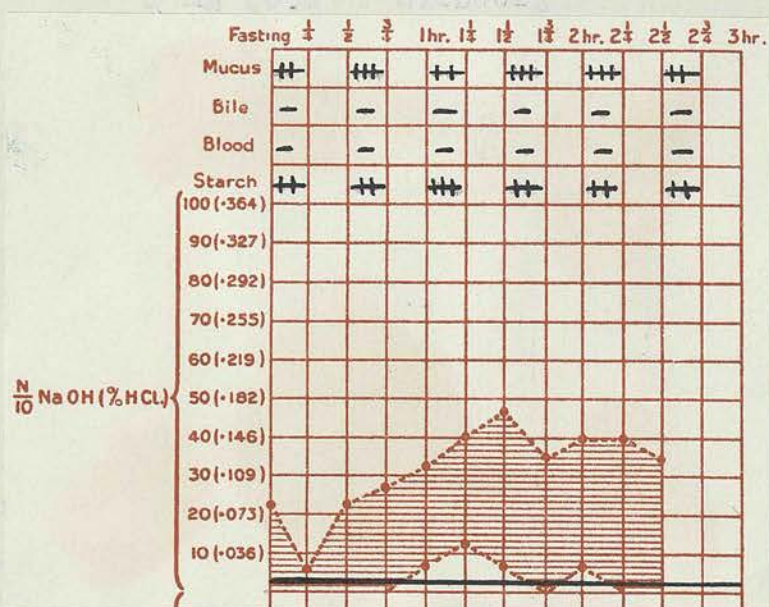
25.1.49 The marrow showed a marked improvement. Far fewer of the megaloblasts could be seen and the basophil reaction of the cytoplasm was less intensive. In many of them some haemoglobin could be detected round the nucleus and the cytoplasm was purple rather than blue. Numerous normoblasts were visible and many more erythrocytes could be seen scattered throughout the marrow than in the previous smears. Normal white blood cell precursors were present.

X - ray Examinations:

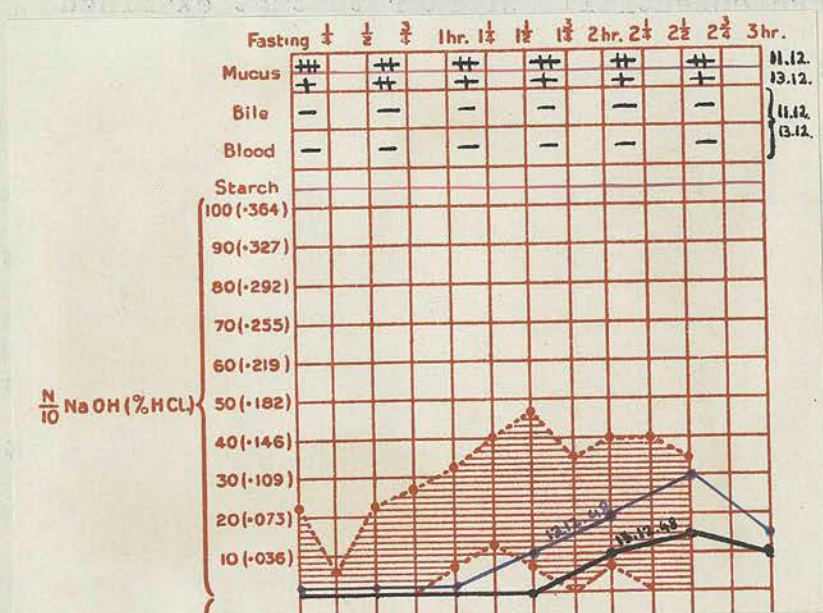
9.12.48 Skull, right femur, lower leg, forearm and wrist:

There is a slight degree of generalised osteoporosis consistent with lack of calcium absorption

EXAMINATION OF GASTRIC SECRETION



9:12:48 Test Meal with Gruel.



11.12.48 } Test Meals with Pronutrin.
13.12.48 }

In every investigation the results are those of the total acid secretion

absorption or utilisation.

2.12.48 Chest, antero-posterior:

There is no definite evidence of pulmonary Tuberculosis.

Estimation of Urinary Chlorides:

In every case the estimation was carried out personally according to the method recommended by Stewart and Dunlop,(1949):

8.12.48 Urinary chloride less than 0.1 gm per 100 cc.

11.12.48 Urinary chloride about 0.3 gm per 100 cc.

14.12.48 Urinary chloride about 0.5 gm per 100 cc.

17.12.48 Urinary chloride more than 0.5 gm per 100 cc.

All subsequent tests gave a value of 0.5 gm or more of chloride per 100 cc urine.

Examination of Gastric Secretion:

Three test meals were carried out soon after the patient's admission to hospital. In the first gruel was given, in the other two pronutrin was given. In each case the acid secretion was found to be diminished and there was an excess of mucus.

9.12.48 Gruel 200 cc.

11.12.48 Pronutrin 200 gm/200 cc.

13.12.48 Pronutrin 200 gm/200 cc.

TREATMENT

The treatment was directed towards the improvement of

- (1) The general health and electrolyte balance of the patient.
- (2) The disordered bowel function.
- (3) The blood condition.

(1) and (2) were treated by resting and by giving him appropriate vitamins and minerals.

It was known from his previous history that folic acid was effective in improving (3) and so it was decided to try to discover if anti-folic acid could inhibit this improvement. Thus from 13.12.48 to 29.12.48 anti-folic acid was given and during six days of this period folic acid was given. The

The effects of the anti-folic acid were assessed and the patient was then given intensive folic acid therapy.

On admission the patient was given a low residue diet containing 120 gms. protein and 50 gms. fat. This was adjusted on 16.12.48 and the adjusted diet was given till the patient was discharged.

16.12.48 Diet:

Low residue

Calories: 2400

Protein: 150 gms.

First Class Protein: 120 gms.

Fat: 60 gms.

Dextrinized carbohydrate: high intake varied in quantity as patient desired.

Vitamin and mineral therapy consisted of giving additional vitamin C, ostelin and calcium lactate, and hepamino in bovril during the period of remission of folic acid.

14.12.48 - 7.1.49 Calcium lactate gr. 150

Ostelin 100,000 units

31.12.48- 4.2.49 Vitamin C 50 mgm. B.I.D.

23.12.48 - 7.1.48 Hepamino:

1 dessertspoonful in Bovril Q.I.D

Folic acid was given for two periods, during the first period anti-folic acid was also given.

Period I

13.12.48 - 30.12.48 Anti-folic acid: daily

16.12.48 - 21.12.48 Folic acid: 5 mgm daily

Period II

7.1.48 - 4.2.49 Folic acid: 5 mgm daily

On his discharge the patient was instructed to continue to take Folic acid : 5 mgm daily. Also arrangements were made for him to get an extra ration of protein and he was instructed to take a high protein, low fat diet in future.

future.

PROGRESS

The patient's progress can be estimated by an evaluation of the following factors:

- (1) His mental state
- (2) His appetite
- (3) Changes in his stools and in the degree of abdominal distension; changes in weight.
- (4) Changes in finger clubbing, muscle tone and muscle reflexes.
- (5) Changes in the skin.
- (6) Changes in the blood picture.

8.12.48 On admission the patient looked tired and listless and did not like to be disturbed. His appetite was fair and he would eat some of the food provided but had no relish for it.

His stool was liquid with no solid matter present, light yellow in colour, of a fatty nature, and had an offensive smell. The degree of abdominal distension has been indicated under the examination.

Finger clubbing, muscle tone and reflexes have been described under the examination.

Skin changes have been described.

Blood picture has been described.

13.12.48 The patient still looks very pale and the yellow tinge to his pallor is still present. However he is now sitting up and taking an interest in the ward; he is also enjoying his food and his appetite is improving. He states that he does not feel so tired as when he was admitted.

There is no change in the stools and the abdominal distension is still present.

Weight: 6 stone 9½ lb.

Roughness of skin and scaling still present.

Hb: 56%

Hb: 56%

Red blood Cell Count: 2,560,000 per cu. m.m.

16.12.48 The patient says he does not feel tired and is becoming hungry. He looks forward to and enjoys his meals. Also he says his stools are not so liquid but this is probably the effect of the charcoal which he has been receiving, since examination of the stools shows them to have very little solid matter in them; (however they are diminishing in frequency). The abdominal distension is still present.

No change in the degree of finger clubbing; muscle tone is still poor.

Limb Reflexes

Upper limb	R	L
Biceps	+	-
Brachio-Radialis	+	-
Triceps	+	+
Lower limb		
Knee	-	-
Ankle	+	+
Plantar	flexor	flexor

Blood Examination: Hb: 49%

Red Blood Cell Count: 2,000,000 per cu.m.m.

17.12.48 Blood Examination:

Hb: 46%

Red blood cell count: 1,620,000 per cu.m.m.

White blood cell count: 5,400 per cu.m.m.

Colour Index: 1.49

Reticulocytes: 2.5%

20.12.48 The patient spends much of his time asleep and has been feeling tired again. His appetite is good and he has asked if he can have some more food.

Stools: He is now passing one or two per day; they are soft but are fully formed and still have some odour.

odour.

Abdominal distension is still present.

Weight: 6 stone 11 lbs.

No improvement in muscle tone.

Limb Reflexes

Upper limb	R	L
Biceps	+	+
Brachio-radialis	+	—
Triceps	—	—
Lower limb		
Knee	—	—
Ankle	+	+
Plantar	?	?

Blood Examination:

Hb: 46%

Red blood cell count: 1960000 per cu.m.m.

White blood cell count: 6200 per cu. m.m.

Colour Index: 1.17

Reticulocytes: 2.6%

Film: Red blood cells show

macrocytosis; a few normoblasts are present.

21.12.48 Blood Examination:

Reticulocytes 7.8%

22.12.48 Reticulocytes 4.8%

23.12.48 Hb: 40%

Red blood cell count: 1,740,000 per cu. m.m.

White blood cell count: 8,800 per cu. m.m.

Colour Index: 1.14

Reticulocytes: 6.5%

27.12.48 The patient is still sleeping for most of the time and feels tired. He is still hungry and always ready for food.

Stools: He is passing one stool each day. It is fully formed but still slightly soft.

soft. There is a slight odour and the stools are light yellow-brown in colour.

Abdominal distension is not so obvious although the whole abdomen is still resonant on percussion.

Weight: 7 stone 4 lbs.

His skin is still thick rough and pale.

Blood Picture

Hb: 58%

Red blood cell count: 3,560,000 per cu. m.m.

4.1.49 The patient does not feel so tired; although ready for his meals he is not so hungry as previously.

Stools: Normal frequency. The odour has disappeared. In colour the stools is yellow-brown.

Abdominal distension is the same as in last examination.

Weight: 7 stone $2\frac{1}{2}$ lbs.

Finger clubbing is still present; muscle tone is improving.

Limb Reflexes

Upper limb	R	L
Biceps	+	+
Triceps	+	+
Brachio-Radialis	+	+
Lower limb		
Knee	—	—
Ankle	+	+

Although some reflexes are still difficult to obtain those present appear to be getting more brisk.

The skin shows no change.

5.1.49 Blood Examination:

Hb: 50%

Reticulocytes: 1.4%

6.1.49

Hb: 54%

Red blood cell count: 2,050,000 per cu. m.m.

White blood cell count: 5,000 per cu. m.m.

Colour Index: 1.31.

Colour Index: 1.31.

Reticulocytes: 1%

7.1.49 White blood cell count: 7,400 per cu. m.m.

Reticulocytes: 2.8%

Packed cell Volume: 24.5%

Mean cell Volume: 128.2 c.μ.

8.1.49 Reticulocytes: 1.3%

10.1.49 The patient says he feels, and looks, very well.

He is eating his food well and normally.

His stools are normal in consistency and smell but the colour is still rather light.

Weight: 7 stone 1½ lbs.

There appears to be some slight ~~clearance~~ decrease in the degree of his finger clubbing but it is very slight.

All his muscle reflexes were obtained, but reinforcement was necessary in order to obtain them in the lower limbs. His muscle tone is improving but it is still not good and his reflexes are still sluggish.

His skin is pale and thick but feels slightly moister.

Blood Examination:

Hb: 52%

Red blood cell count: 1,910,000 per cu. m.m.

Colour Index: 1.36

11.1.49 Reticulocytes: 2.1%

12.1.49 Reticulocytes: 5.2%

14.1.49 Hb: 72%

Red blood cell count: 2,510,000 per cu. m.m.

White blood cell count: 12,600 per cu. m.m.

Colour Index: 1.4%

Reticulocytes: 4.5%

15.1.49 Hb: 72%

Red blood cell count: 2,510,000 per cu. m.m.

White blood cell count: 12,600 per cu. m.m.

Colour Index: 1.29

Colour Index: 1.29

Reticulocytes: 2%

17.1.49 The Patient feels very well. He has been getting up and walking round the ward. His appetite is normal.

Stools: normal

Weight: 7 stone $3\frac{3}{4}$ lbs

The patient's skin feels softer and more moist than when he came into the ward; also his fingers do not seem to be so swollen.

Muscle tone is still very weak but reflexes can all be obtained without reinforcement.

24.1.49 The patient began getting up in the afternoons.

Weight: 7 stone 7 lbs 6 ozs.

Blood Examination:

Hb: 74%

Red blood cell count: 2,670,000 per cu. m.m.

White blood cell count: 8,400 per cu. m.m.

29.1.49 The patient has started to go out for walks in the afternoons.

31.1.49 Weight: 7 stone $7\frac{1}{4}$ lb.

Blood Examination:

Hb: 80%

Red blood cell count: 3,550,000 per cu. m.m.

White blood cell count: 13,200 per cu. m.m.

Colour Index: 1.21

Reticulocytes: 41%

2.1.49 The patient is very well. His cheeks show some colour, his mucuous membranes are red and he looks energetic and not at all tired.

He is eating all his meals, and his stools are normal.

Muscle tone is much better than when he was admitted but it still appears to be slightly less than normal. His reflexes

reflexes could all be obtained but are not as brisk as normal.

His skin is still slightly rough and pale. But it is slightly moist and is not scaling in the skin creases as it was on admission.

There is still a faint blowing systolic murmur in the mitral area which is not propagated.

Blood examination shows a macrocytic type of **anaemia** with a colour index above unity and a bone marrow still of a megaloblastic type though it shows improvement when compared with its state on admission.

4.1.49 Discharged.

DISCUSSION.Diagnosis.

This case has been diagnosed as malabsorption syndrome because though the clinical features are those of tropical sprue, many of the physiological changes and the pathological conditions which are exhibited are attributable to intestinal dysfunction and malabsorption. It is the disturbed state responsible for these features which will be discussed in particular.

The malabsorption may have been associated with other conditions than sprue. The patient suffered from an acute attack of bacillary dysentery while he was in South Russia, and also from food poisoning while he was in Persia. The history of the former condition is typical of bacillary dysentery. In spite of effective treatment at the time, the patient might well have become a carrier and the clinical features may now be due to chronic bacillary dysentery. The absence of any blood or of any dysenteric organisms in the stools, together with the very severe megaloblastic anaemia, make a diagnosis of dysentery untenable. The response to folic acid therapy and the period of apparent recovery since discharge from Evesleigh are not characteristic of dysentery.

Amoebic dysentery is commonly present in people returning from India and the Middle East. In this patient the stools, blood picture, and bowel symptoms are not characteristic of this disease. However, in view of the possibility of amoebic or bacillary dysentery being present in a subacute form, and since it is known that they often are aetiological agents in the/

the onset of sprue, it would have been advisable to have carried out a sigmoidoscopic examination. Idiopathic ulcerative colitis is not associated with the kind of stools found in this case and the same objections to a diagnosis of this condition can be raised as to a diagnosis of dysentery.

The absence of a history of gastric ulcer or of abdominal wounds, or of chronic dysentery, make it unlikely that the clinical features could be caused by an intestinal short-circuit. Pain and constipation and the passage of blood in the stools are characteristic of diverticulitis, but the history and clinical features of the illness in this patient are not otherwise typical of this condition.

Each of these intestinal diseases would have been eliminated from the list of possible diagnoses by a barium enema. In malabsorption syndromes also, characteristic radiographic appearances may be discovered. There is often loss of tone and diminution of peristaltic action and the terminal coils of the ileum may be greatly dilated. The lumen of the bowel is distended, and the normal delicate feathery pattern of the gut is replaced by one of coarser texture. Even though the conditions mentioned above can be eliminated by history and clinical features of the illness, radiological examination of the bowel might have shown some abnormalities and would have indicated the chronicity of the disease.

Intestinal tuberculosis with involvement of the lymph vessels and glands produces signs and symptoms very similar to those shown in this case. Diarrhoea is common and is due to hypermotility of the bowel wall caused by involvement of Auerbach's plexus and appears as a result of tuberculous involvement of the lymph vessels. If this occurs, there is malabsorption of fats with resultant diarrhoea and fatty stools, and/

and also malabsorption of other food from the gut. If there is involvement of the mesentery, there is ascites or a plastic exudate with abdominal swelling. The general symptoms of the disease produce the loss of weight, tiredness, and weakness. However, even if the malabsorption was extreme it is unlikely that such a great degree of anaemia could be produced as there was in this case. Diagnosis of intestinal tuberculosis is made by the use of abdominal X-rays, which show hypermotility, spasm, and filling defects, by X-ray of the chest to exclude pulmonary tuberculosis, and by tuberculin tests. Pulmonary tuberculosis was excluded in this case, and the history and clinical examination were considered sufficient evidence to exclude abdominal tuberculosis and diagnose sprue.

It has been suggested that there is some affinity between tropical sprue and allied diseases such as idiopathic steatorrhoea, coeliac disease, pellagra and pernicious anaemia. In these diseases the blood pictures may bear some resemblance and the malabsorption of carbohydrates and fats are responsible for many of the clinical features. These diseases will be discussed under pathology.

Aetiology.

In malabsorption syndromes attention has been focussed on the alimentary tract when attempting to find an aetiological factor. In tropical sprue it has been observed that its onset is very often preceded by an attack of bacillary dysentery. It is unknown why this should predispose to tropical sprue. This patient developed bacillary dysentery while he was in South Russia after the onset of the sprue. The sprue began after eighteen months heavy labour on a very restricted diet and it was not till thirteen months later that he developed dysentery. It is said that the phenomena of sprue can best be explained in terms/

terms of a metabolic derangement of the gastro-intestinal tract characterized by a disturbed absorption in the small intestine in some way connected with defective secretion of Castle's intrinsic factor by the pyloric glands. It has been shown that nicotinic acid and riboflavin are essential for normal fat absorption and, further, that the villi and crypts of Lieberkuhn contain anti-pernicious anaemia factor. Thus a deficiency of Vitamin B might well interfere with the normal function of the intestine and possibly with the absorption of the specific anti-anaemic factor (S.A.F.). The patient was living on a very deficient diet before the onset of sprue and this alone may have been sufficient to cause such damage to the intestinal wall as to disturb its function, in the same way as bacillary dysentery does in other people. The subsequent development of bacillary dysentery probably affected adversely the progress of the sprue, but in this patient it appears that the deficient diet was the primary aetiological agent. The patient's diet was obviously deficient in many ways but it is of interest to note that at no time did he complain of sore tongue or definite skin symptoms. Vitamin B deficiency thus cannot have been gross. However, it was found that in prisoners suffering from gross vitamin deficiencies during the last war, it was only when there was a relative lack of one of the factors of the B complex that symptoms appeared. If all the B complex was deficient, symptoms were not so severe; it is possible that this occurred in this patient.

Pathology.

The features of tropical sprue which are responsible for the signs and symptoms, and which it is the aim of treatment to cure, are those associated with the disorder of the gut, the blood disorder and the pathological lesions in the mouth and skin which/

which, though not obvious in this case, are considered to be characteristic of sprue and of pernicious anaemia, coeliac disease and the steatorrhoeas .

In this patient red cell formation was arrested at the megaloblastic stage. Examination of the sternal marrow showed it to be full of megaloblasts with some normoblasts and few erythrocytes. As a result of treatment with folic acid, the number of megaloblasts was reduced and the normoblasts became more numerous.

Normal red cell formation is only possible if certain factors are obtainable. S.A.F. is stored in the liver. It is formed as a result of the inter-action of a factor in the food, found in liver, beef myoglobulin and yeast, with a factor secreted by the fundus and cardia of the human stomach known as haemopoietin. Anti-anaemic potency is well-marked in the jejunum and ileum; this activity of the intestines may be due to adsorbed S.A.F. in the process of absorption. Once absorption has occurred, the S.A.F. is stored in the liver from which it can be extracted by a method similar to that used for extracting anti-pernicious anaemia principle formed by the incubation of haemopoietin and beef protein. Wilkinson (1948) is of the opinion that haemopoietin is an enzyme, secreted by the gastric mucosa. None of the known factors of the Vitamin B complex can act as the extrinsic food factor either alone or in combination, although nicotinic acid appears to influence the formation of S.A.F. (Petri, 1944). It has been suggested that pteroyl poly glutamic acid may be the extrinsic factor which, as a result of the enzymic action of haemopoietin, or by the action of liberating factors in the liver, may be deconjugated to form pteroyl glutamic acid or folic acid, which may be the S.A.F. or at least play an essential part in the haemopoietic mechanism.

Wilkinson/

Wilkinson does not agree with this suggestion and considers that folic acid only plays a minor role in haemopoiesis. However, it is on the basis of these suggestions that folic acid is used in the treatment of megaloblastic anaemias. In megaloblastic anaemias the normal red blood cell maturation is disturbed, the pro-erythroblast, instead of forming the normoblastic series, develops into an early megaloblast and thence through the megaloblast series into the megalocyte. As a result, in this patient, sternal puncture showed abnormal haemopoiesis with large numbers of megaloblasts. Following folic acid therapy, maturation became normal and normoblasts reappeared in the films.

Pernicious anaemia is characterised by complete achylia gastrica, with deficient secretion of haemopoietin. In sprue there may be a reduction of gastric secretion, as in this patient, but there is no achylia gastrica and there is normal secretion of haemopoietin but failure of absorption of S.A.F. (Wilkinson, 1949). In pernicious anaemia it is very rare for the gastric secretion to become normal; in sprue the abnormal gastric secretion may only be temporary and improvement may take place, as eventually occurred in this patient.

Nicotinic acid and riboflavine deficiency result in stomatitis and changes in the tongue. Diarrhoea is common and skin lesions may occur. With nicotinic acid deficiency the skin is first red and itchy and later desquamation occurs and the underlying skin remains abnormally thickened and pigmented. In riboflavine deficiency there is angular stomatitis and a seborrhoeic condition round the ears and nose. As stated above, nicotinic acid may have some effect on the formation of S.A.F. in the stomach and these two vitamins appear to have some relation to the adrenal cortex, which is concerned with the phosphorylation by which fats and glucose are absorbed in the gut./

gut. In sprue the skin and oral lesions due to deficiency of nicotinic acid and riboflavin are generally present and many of the clinical features of the condition are associated with the disturbances of metabolism caused by their absence. In this case the signs of their deficiency were not marked. The skin was pale and thickened over the hands and feet and there was a small scaling area on the right cheek. There were no lesions in the mouth. Diarrhoea was present but Sheldon (1948) gives an explanation for this which does not involve Vitamin B. Presumably in this case Vitamin B deficiency did not play an important part. If it had done, intensive Vitamin B therapy would surely have been necessary and improvement would not have occurred so easily and rapidly on rest, a high protein diet and folic acid.

Coeliac disease and idiopathic steatorrhoea resemble sprue in having the symptom of diarrhoea, with the passage of an offensive liquid stool with a high content of split fat. The fact that the fat is split means that fat digestion is normal but that it is the absorption which is at fault. In the past the alimentary disturbance has been attributed to this mal-absorption of fat and therapy has consisted in the administration of a diet low in fat as in this case. These conclusions were based on estimations of the faecal fat. The use of fat-balances have shown that faecal fat estimations are often of little value. Fat balances show that even if the amount of faecal fat were doubled a large proportion of the ingested fat would still be absorbed. Thus unless it can be shown that the increased intestinal content of fat does harm, it does not seem justifiable to cut down the ingestion of fat. The abnormal distension in this group of diseases is probably caused by excessive fermentation of carbohydrate, and the diarrhoea is attributed to the same cause. In spite of this suggestion by Sheldon/

Sheldon, emulsifying the stools with iodine did not produce any colour. However, this may have been because digestion of the carbohydrate had produced molecules too simple to react with iodine to produce coloured compounds. Thus it seems that attention should be directed towards glucose absorption and metabolism and the parts which Vitamin B and the adrenal cortex play in this, rather than towards estimations of faecal fat which appears to vary greatly and bear little relation to fat absorption as shewn by fat balances.

In sprue, absorption of proteins appears to be normal. Protein absorption does not depend on phosphorylation like that of fats and carbohydrates, and for this reason a high protein diet is given. Shortly after admission the plasma albumen was found to be diminished and the globulin relatively raised. Twenty-four days later the plasma proteins were almost normal although during this period treatment had consisted of the administration of folic acid and anti-folic acid, Vitamin D and calcium lactate and a high protein diet. Since the action of the folic acid was inhibited by the anti-folic acid, it must have been the high protein diet alone which caused the improvement in the plasma proteins which had probably been reduced by the use by the body of protein for energy during the period of malabsorption of carbohydrate and fat.

Tetany commonly accompanies sprue and is due to malabsorption of calcium and phosphorus, or to disturbance of the acid-base balance of the blood. The serum calcium was below the normal level all the time that the patient was in hospital, and though it finally did increase slightly, it never entered the normal range. The serum calcium was the last of the biochemical estimations to show a return towards normal - about three weeks after the alkaline phosphatase and plasma proteins had become normal. The urinary chloride excretion reached a normal value before/

before any of the other biochemical estimations showed a change. A generalised electrocyte disturbance was present which an attempt was made to rectify by suitable dietetic treatment. Manson-Bahr (1943) concludes defective absorption is the basic factor involved in the low-calcium content of the blood and that in these circumstances a low fat dietary, calcium salts and irradiated ergosterol are indicated. This treatment is directed toward the rectification of biochemical changes by replacement therapy, although the mechanism of why the biochemical changes occurred is unknown, apart from the rather vague term of "malabsorption". It seems that in this disease the defective absorption is due to an abnormality in the mechanism by which absorption is carried out by the gut wall rather than by a dietetic deficiency, and that suitable dietetic therapy by restoring this mechanism enables a subsequent return to normal of the blood chemistry. Disturbed calcium metabolism may result from malabsorption of the fat soluble Vitamin D which can be expected in the presence of disturbed fat absorption. Measures were taken to prevent the onset of tetany, but there was obviously some disturbance of electrolyte metabolism as shown by the diminished chloride excretion. This rapidly improved when the diet was controlled, but it improved before the diarrhoea disappeared and so it cannot wholly have been due to loss of chlorides as a result of malabsorption due to intestinal hurry. Disturbance of chloride metabolism would be associated with other disturbances of electrolyte metabolism. Electrolyte metabolism is controlled by the suprarenal cortex and this disturbance may be associated with cortical dysfunction which may also be an aetiological factor in the disturbed carbohydrate and fat metabolism.

The disturbed physiology of this disease can be summarised in/

in terms of the principal clinical features:

(a) The disordered bowel function. This results in sub-normal values for various chemical compounds in the body, with subsequent disturbances of metabolism. The reason for the malabsorption is unknown but is probably partly due to intestinal hurry and partly to disturbance of function in the gut wall. The fact that diarrhoea may cease long before normal blood levels are reached, and that other chemical estimations may return to normal while the diarrhoea is still present, indicates that intestinal hurry cannot account for the whole of the malabsorption. Folic acid treatment has a variable effect on the diarrhoea which may improve, remain unaffected, or become worse (Manson-Bahr, 1948).

(b) The anaemia. The reason why this occurs is now known, but the factor necessary for the maturation of the blood cells has not yet been identified. Folic acid produces an improvement of the anaemia although it is probably not S.A.F. By administering folic acid, effective substitution therapy is carried out, and the anaemia can be improved. In this patient the anti-folic acid prevented improvement of the blood picture but had no effect on the improvement of the diarrhoea. The diarrhoea improved independently of the folic acid, presumably because of the dietetic therapy.

Treatment.

Treatment consisted of folic acid therapy, which is known to be effective in treating the anaemia, and dietetic treatment in an effort to increase absorption of minerals, vitamins and other factors which chemical examination showed to be deficient.

The administration of anti-folic acid was carried out to determine whether it could block the action of folic acid in improving the blood picture. This it did effectively and thus/

thus it may be concluded that the folic acid therapy did not start until 7.1.49, by which time the weight had shown a significant increase, the stool had become normal and the biochemical estimations had returned to normal. It would thus seem that the folic acid played little part in restoring the bowel to normal although it was essential for the resumption of a normal blood picture, as shown by the marked reticulocyte response and change in the bone marrow during Period II.

Since it could not be assumed that normal bowel function had been restored, dietetic therapy had to be continued after discharge. Remission of folic acid is known to result in a relapse of the blood condition, presumably due to continued inability to absorb S.A.F. This is further evidence that bowel function is still abnormal, and therefore folic acid therapy had to be continued after discharge.

Folic acid is more effective than liver in the treatment of sprue, but the latter was given in this case between the periods of folic acid administration, in the hope that it might supply some of the factors necessary for the improvement of the condition and also in order to maintain the patient's improvement while folic acid was withheld.

Conclusion.

As a result of treatment, this patient's condition was alleviated. Cure was not produced and treatment will have to be maintained probably for the rest of his life. Treatment with folic acid causes an improvement in the blood picture, and dietetic treatment improves the patient's general condition. In spite of this there is still some residual bowel dysfunction. During his illness there was a profound disturbance of electrolyte metabolism. Treatment produced a gradual improvement of this but, even if treatment is maintained, it is known that osteoporosis/

osteoporosis and disturbance of the calcium, phosphorus and chlorides of the body, in many cases of sprue tend ultimately to become of a chronic nature, and are responsible for much subsequent ill-health. The long history in this case of ill-health in the absence of proper treatment, and of relapses even in the presence of effective treatment, adequately indicate that folic acid is not an entirely satisfactory form of therapy and that, until the underlying metabolic disturbance is discovered, treatment cannot be perfect.

An attempt was made during the treatment of this patient to investigate the underlying metabolic disturbance. An experiment was performed in order to discover whether anti-folic acid is an effective antagonist to folic acid. Such an experiment must be carefully controlled; control in this case consisted of:

1. A careful control period to obtain basal conditions in the absence of therapy by either drug. During this period no changes in the blood picture occurred.
2. The administration of the anti-drug for a period (Period I) during part of which the folic acid was also administered. During this period observations were carried out on the blood to discover if any changes occurred.
3. The administration of the folic acid alone. Observations on the condition of the blood were continued and, after five days treatment, the time over which the folic acid had been given during Period I, a reticulocyte response had been obtained together with an improvement in the blood picture. It could thus be concluded that anti-folic acid effectively blocked the action of folic acid in improving the maturation of the blood.

Every/

Every therapeutic measure is essentially an experiment, since no two patients react in exactly the same way. This is illustrated by the variations in dosage and variations in response observed in different patients. In this case a new drug was investigated, some knowledge was gained concerning its therapeutic effect. It is by such investigation that knowledge can be gained on the mechanism of disease by the use of the experimental method; by the application of the results, thus obtained, to other patients advances in therapeutics are made.

CASE II

PROFESSOR D. M. DUNLOP

MRS. AGNES GILROY

Ward 21,

Royal Infirmary

of Edinburgh.

DIAGNOSIS: ENDOCRINE DISTURBANCE ASSOCIATED

WITH THE MENOPAUSE.

MRS. AGNES GILROY

aet. 51 years married,

19, Minto Place,

one daughter.

Hawick.

Occupation: Housewife

Doctor: Dr. Scott,

Hawick.

Date of Admission: 24.11.48

Date of Examination: 25.11.48

Date of Discharge: 16.12.48

Complaint: Flushing for two years; rapid and severe swelling of the neck for two months.

HISTORY

History of Present Illness

The patient had her last period in August 1946; the blood loss was reduced, but otherwise the period was normal in character. Preceding this, she had noticed that her blood loss at each period had been getting less for the last two or three months although she had had no inter-menstrual bleeding. During this period she had noticed the onset of flushing which occurred mostly at night and appeared once or twice every twenty-four hours. The flushes appeared first in her lower limbs and consisted of a pricking sensation and feeling of warmth associated with a little sweating. The flush slowly passed up her body and disappeared last from her forehead and face. The flushing did not disturb the patient very much and during the following nine months its frequency and severity diminished until it had almost entirely disappeared. During this period the patient noticed no change in weight and had no other symptoms; there was no further vaginal blood loss.

In August 1947 the flushing began to increase in severity and frequency. She began to have three or four flushes per day but was not particularly troubled with them at night.

night. In November, the patient began to feel very tired and began to find that her household duties were becoming a burden and a worry to her. She became irritable and her husband remarked on it, although she felt that she had been losing control of herself too easily during the whole preceding year. At this time she had not noticed any changes in her eyes or neck. In January 1948 although physically she felt well she noticed that she was becoming very thin and her friends also noticed it. She developed a huge appetite and she never seemed to have had enough food; she said that she felt that she could always eat another meal immediately after finishing a meal although she always ate more than the rest of the family at each meal. She became very nervous and "jumpy", developed a tremor in her hands and noticed that a swelling had appeared in her neck. She did not feel warm and her skin did not sweat excessively, although the flushes still occurred three or four times a day and were becoming more severe. She was sleeping very little at this time and ^{her} average night's sleep was only about three or four hours. She went to see her doctor in February who prescribed iron tablets which she continued to take for three or four months. These had the effect of alleviating the shortness of breath from which she had been suffering in January even when she performed very slight movements or exerted herself to the least extent. From January until June these symptoms continued and became more severe so that in March and April particularly she felt tired, nervous, worried and physically she seemed to be wasting away. In June she took her daughter to see the doctor who remarked again on her excessive thinness and tiredness; he examined her and referred her to the R. I. E.

Thiouracil was prescribed, of which she was told to take 0.2 gm. three times a day; this dose was reduced at the end

end of August to 0.2 gm. daily. The patient began to gain weight, to become less irritable and to sleep better. The symptoms continued to improve throughout the summer although the patient's flushes did not seem to be affected. By the beginning of October she noticed that her neck was swelling rapidly and at the end of the month it had become very large, and she was complaining of pain down the inner side of her right arm and in her neck. She also noticed that large pouches had appeared below her eyes. She was seen again at the R. I. E. at the end of October when her name was put on the waiting list for admission to ward 21, and her dose of thiouracil was reduced to 0.1. gm. daily. The patient often feels warm and she sweats a good deal and prefers the colder weather. She has had no urinary or bowel symptoms.

Previous History

The patient has been a very healthy woman. She has never had rheumatic or scarlet fever. Thirteen years ago she was in the R. I. E. for treatment for haemorrhoids and her symptoms were all^eviated. Her periods have always been regular and normal and her daughter was born with no difficulty.

Family History

The patient's husband is alive and well, and works as a railway signalman.

Daughter, aged eleven is alive and well.

Father died of colitis in 1933 aged 63.

Mother died aged 63.

Social History

The patient, her husband and daughter live together in a small house outside Hawick. They are very happy together and comfortable. They get sufficient food and their rations are supplemented by farm produce.

SUMMARY OF CLINICAL FINDINGS PRIOR TO ADMISSION

23.6.48 Examination in M.O.P.D., R. I. E.,

R. I. E.

A diagnosis was made of toxic adenoma of the thyroid with pronounced cardio-vascular symptoms. Her heart was much enlarged and her blood-pressure was raised.

14.7.48 Examination in M.O.P.D., R. I. E.

The patient feels better and has put on 6 lbs. in weight. She weighs 7 stones.

Pulse - Rate: 92/minute.

27.8.48 Examination in M.O.P.D., R. I. E.

The patient has put on 12 lbs. in weight, is not so nervy and shows much improvement.

Pulse - Rate: 82/minute, regular.

30.10.48 Examination in M.O.P.D., R. I. E.

The thyrotoxicosis has much improved but the thyroid has increased in size very much.

Summary of Treatment Prior to Admission

23.6.48 0.2 gms Methyl Thiouracil T.I.D.

14.7.48 0.2 gm Methyl Thiouracil daily.

Phenobarbitone gr. 1 nocte.

26.8.48 0.2 gm Methyl Thiouracil daily.

30.10.48 0.1 gm Methyl Thiouracil daily.

PHYSICAL EXAMINATION

General Inspection

A small intelligent but rather lethargic woman sitting up in bed. Her skin is pale and slightly yellow. She has thick black eye-brows with large dark pouches under her eyes. She has a long and rather puffy face and looks tired. Her neck is very swollen. Her hands are warm and sweating but there is no clubbing or cyanosis of her fingers and her skin does not feel oedematous.

Temperature: 97.4 ° F

Actual Weight: 7 stone 3 lbs.

Ideal Weight: 9 stone 12 lbs.

Height: 5 foot 2 inches.

Cardio-Vascular System

Pulse:

Regular in rhythm and volume. Vessel wall impalpable; pulse wave well-sustained.

Rate: 90/minute.

Blood Pressure: 150/92.

Precordium

There is no venous congestion or pulsation visible in the neck. The apex beat can be seen just outside the mid-clavicular line. On palpation, pulsation can be detected over the swelling of the neck and more strongly in the supra-sternal notch. The apex beat is in the fifth intercostal space, $3\frac{3}{4}$ inches from the mid-line just outside the mid-clavicular line. On percussion, the area of cardiac dullness is slightly increased along the left border:

in the 3rd inter-space it is $2\frac{1}{2}$ inches from the mid-line

in the 4th " " " " 3 " " " " "

On auscultation; the heart-sounds are closed and pure.

Respiratory System

The chest is normal in shape and the subcostal angle is normal in size. Nothing abnormal detected on examination.

Respiration Rate: 22/minute.

Alimentary System

Mouth:

Tongue: clean and moist.

Teeth: false but well-fitting.

Tonsils and oral Pharynx: Nothing abnormal detected.

Abdomen

No pulsation or swelling detected. The respiration is only slightly abdominal.

On examination the abdomen is soft and nothing abnormal can be detected.

Central Nervous System

Central Nervous System

Mental State:

The patient is fairly intelligent but rather reserved and tends to be of a worrying personality. She is co-operative and interested in the state and progress of her condition.

Cranial, Spinal Motor and Sensory Nerves:

Nothing abnormal detected.

Reflexes:

The conjunctival, palatal, and abdominal reflexes are brisk. Plantar reflexes are flexor.

Deep reflexes:

Upper Limbs:

	Right	Left
Biceps	+	+
Brachio-radialis	+	+
Triceps	+	+

Lower Limbs:

	Right	Left
Knee	+	+
Ankle	+	+

All the reflexes are brisk.

Trophic changes and Muscle Coordination:

No trophic changes.

There is a slight tremor in her fingers and hands when she extends her arms in front of her.

Endocrine System

Thyroid Gland:

The gland is much enlarged and gives the neck a broad rounded appearance which is more particularly marked on the right side. The isthmus is thickened and diffusely enlarged. The right lobe extends up to a point level with the upper margin of the thyroid cartilage; it can be felt protruding from behind the posterior border of the sterno-mastoid and

and inferiorly the lower pole extends down below the upper margin of the sternum. The left lobe is not so large, and can just be felt behind the left sterno-mastoid and its lower pole can be felt above the sternum. The enlargement feels hard and regular in the right lobe and is probably due to the presence of a large adenomea. The isthmus and left lobe are regularly enlarged although one or two small lumps can be detected where the isthmus joins the lobe.

Pulsation can just be detected over the lower right portion of the gland and the arterial pulse can be heard over the gland. Diameter of the neck at the level of the lower border of the Thyroid cartilage: $15\frac{1}{4}$ inches.

Lymph Glands:

No glands can be detected in the cervical, submaxillary or submental regions. There are a few small superficial glands in the groins. There are two small distinct glands in the right axilla.

Mammary Glands:

Both breasts contain stringy, lumpy tissue in relation to the nipples and extending up into the axillary tails. This tissue is within the mammary substance and is not attached to the deeper tissue or the skin. The mammary glands feel atrophic.

Skin and Subcutaneous Tissues

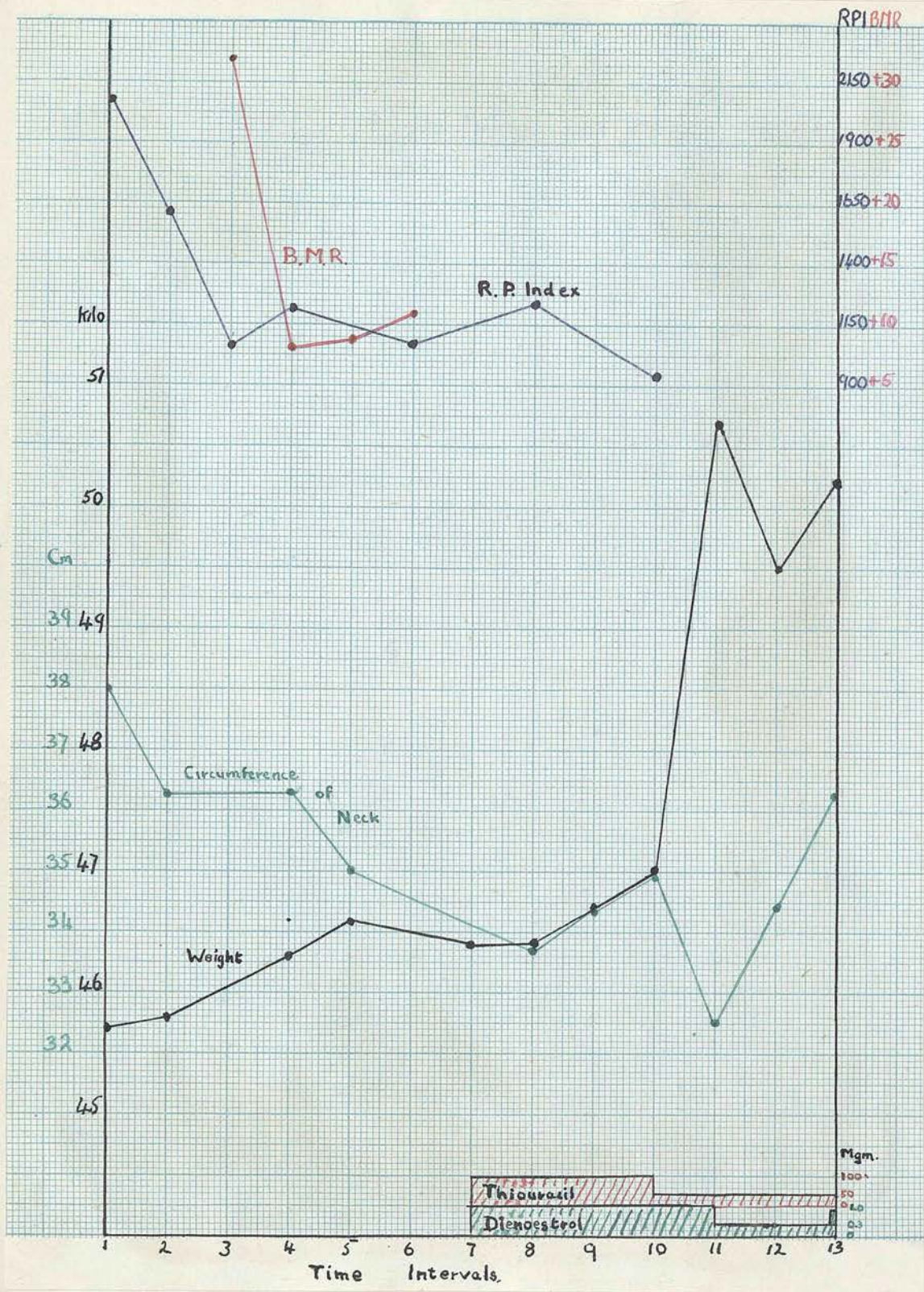
The skin is pale and has a slightly yellow colour. Over the trunk and hands the skin is soft, warm and is slightly moist, although the patient does not think it is any more moist than usual. The skin is elastic and healthy, but there is scanty subcutaneous tissue. There are large dark-coloured pouches under both eyes.

Locomotor System

Muscles : Power normal and equal.

Joints: Nothing abnormal detected.

Blood Examination



The graph shows the patient's progress from the time that she was admitted to hospital. It illustrates how the physical findings changed relative to one another; for this purpose the horizontal scale is divided into equal time intervals which correspond to the dates mentioned in the Progress Report.

TIME INTERVAL	DATE	TIME INTERVAL	DATE
1	24.11.48	8	11.12.48
2	28.11.48	9	14.12.48
3	30.11.48	10	16.12.48
4	1.12.48	11	14.1.49
5	3.12.48	12	15.2.49
6	6.12.48	13	11.3.49
7	7.12.48		

The R.P. Index is the product of the Pulse and Respiration Rates. According to Bene (1949) this Index varies according to the B.M.R. The normal values for the R.P. Index lie between 1100 and 1500.

Blood Examination

Examination of the Blood:

Hb: 95%

Red blood cell count: 4,640,000 per cu. m.m.

White blood cell count: 4,800 per cu. m.m.

Wasserman Reaction: negative.

Special Examinations

1.12.48 B. M. R. + 32%

3.12.48 B. M. R. + 8%

6.12.48 B. M. R. + 9%

7.12.48 B. M. R. + 11%

TREATMENT

The treatment was guided by the following considerations:

- (1) The need for a period of observation and rest to determine the exact nature of the pathological condition, and to see to what extent spontaneous recovery would occur under controlled and basal conditions.
- (2) When the underlying cause for the derangement of thyroid function had been determined, the control of the condition by suitable drug therapy.

24.11.48 Phenobarbitone gr. 1 B.I.D.

Cyclobarbitone gr. 3. at night.

25.11.48 Discontinue Phenobarbitone.

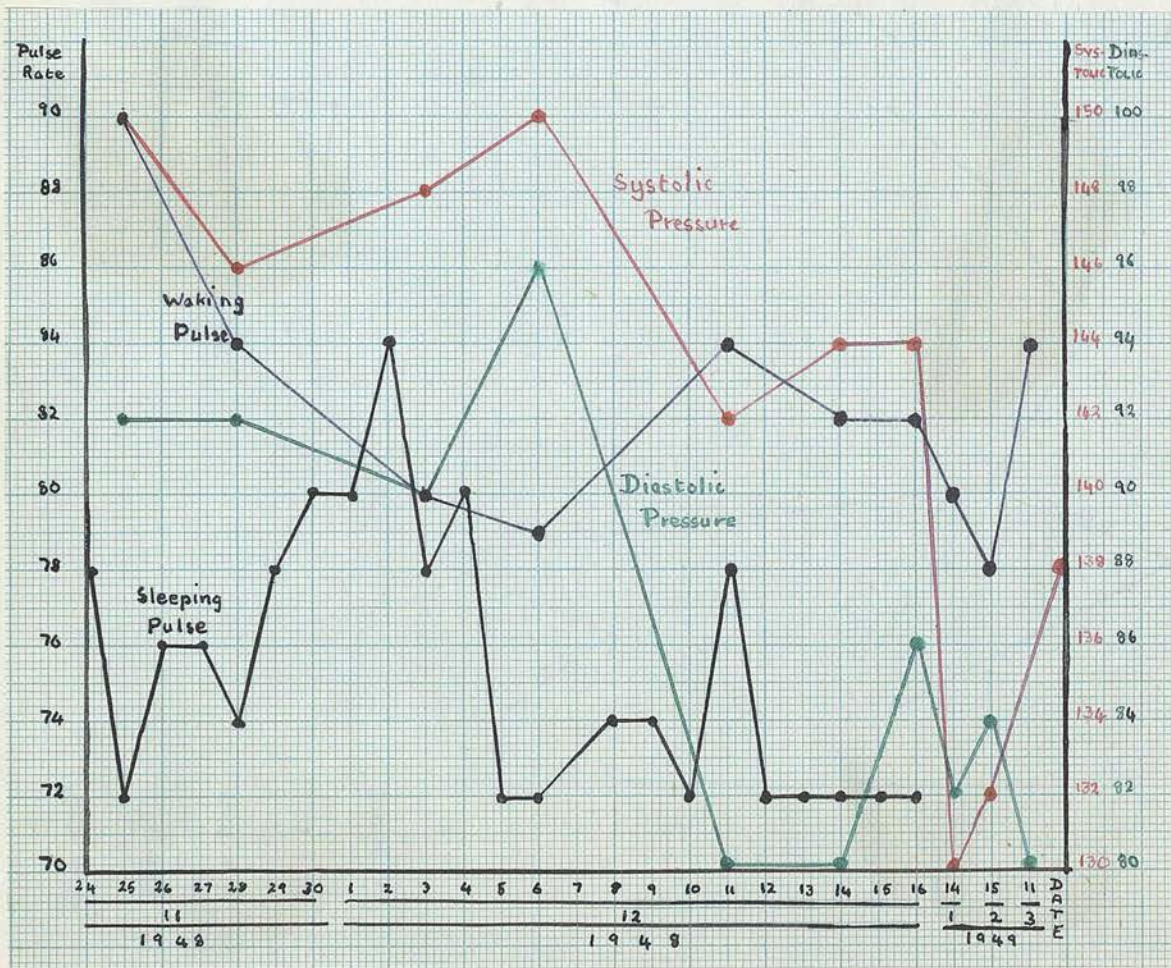
8.12.48 Dienoestrol 1.0 mgm. daily.

Methyl Thiouracil 0.1 gm. daily.

PROGRESS

The patient's progress in hospital was measured by

- (1) The change in weight.
- (2) The circumference of the neck.
- (3) The change in pulse rate and Blood Pressure.
- (4) The appearance of flushings.
- (5) The change of degree of tremor in her hands and examination of her deep reflexes.



(6) Her general appearance.

The changes in weight, circumference of her neck, pulse and respiration rates, and blood pressure are shown in the table.

28.11.48

Weight: 7 stone 4 lbs.

Circumference of neck: $14\frac{1}{2}$ inches.

Pulse Rate: 84/minute.

Blood Pressure: 146/92.

She has had two or three flushes each day, but it does not worry her so much at night.

The tremor is still almost as much as when the patient was admitted but she states that she feels much better, is sleeping well and does not feel so nervous. Her reflexes are brisk. The patient still is pale and she has large pouches under her eyes. She takes her food well and reads and sleeps most of the time.

3.12.48

Circumference of neck: $14\frac{1}{2}$ inches

Pulse Rate: 80/minute

Blood Pressure: 148/90

The tremor in her hands is as noticable as when she was admitted and her reflexes are brisk. She looks much better and less tired and her face is fatter and not so anxious.

6.12.48

Weight: 7 stone $3\frac{3}{4}$ lbs.

Circumference of neck: 14 inches.

Pulse Rate: 79/minute.

Blood Pressure: 150/96

She is still affected by flushing but she says it is not so frequent as when she first came in.

Reflexes still brisk but those in lower limbs are less vigorous than formerly. The pouches under her eyes are much smaller, and she has a little red colour in her cheeks.

11.12.48

Circumference of Neck: $13\frac{1}{2}$ inches

Pulse Rate: 84/minute

Blood Pressure: 142/80

14.12.48

Weight: 7 stone 4 lbs.

Circumference of neck: $13\frac{3}{4}$ inches.

Pulse Rate: 82/minute.

Blood Pressure: 144/80.

She thinks that the flushing is getting better and is certainly not so frequent as formerly; also the severity of each attack is much less.

The tremor has almost entirely disappeared and her deep reflexes though still brisk are within the limit of normal.

Her face is quite fat and she no longer looks tired; the pouches under her eyes have almost disappeared. Her skin is warm and still slightly moist.

16.12.48 Discharged.

Circumference of Neck: 14 inches.

Pulse Rate: 82/minute.

Blood Pressure: 144/86.

Subsequent Progress

The patient was discharged home on

0.05 gm thiouracil daily.

1 mgm dienoestrol daily.

14.1.49

Weight: 7 stone $13\frac{1}{2}$ lbs. clothed.

Circumference of Neck: 13 inches.

Pulse: 80/minute.

Blood Pressure: 130/82

Her flushings are much reduced and she has not had any for about a week. She feels very well and is not tired or nervous. Her face has some colour and does not look puffy.

puffy.

She was told to take

Thiouracil 0.05 gm. daily.

Dienoestrol 0.30 mgm. B.I.P.

15.2.49 Weight: 7 st. $11\frac{1}{2}$ lbs.

Circumference of Neck: $13\frac{3}{4}$ inches.

Pulse: 78/minute.

Blood Pressure: 132/84

Her flushings have now become very infrequent and slight. Her neck has increased in size but is not now as large as it was earlier in the month. Her neck feels soft and she has had no symptoms of pressure by the goitre. She has had some vaginal bleeding and more tingling in her breasts. This was present for a week. Otherwise she feels very well.

Her therapy was not changed.

11.3.49 Weight: 7 st. $12\frac{1}{2}$ lbs.

Circumference of Neck: $14\frac{1}{2}$ inches.

Pulse: 84/minute.

Blood Pressure: 138/80

She has had no more flushings. Her neck has again increased in size and she says it varies in size very much; she may notice a distinct change in size even over-night. It is soft and has given no symptoms of pressure. She has had no more vaginal bleeding and feels very well.

She was told to take

Dienoestrol 0.9 mgm. daily.

Thiouracil 0.05 gm. daily.

DISCUSSION.

Diagnosis.

The diagnosis of an Endocrine Disturbance associated with the Menopause was made in this case, because, though the patient initially suffered from the symptoms of Thyrotoxicosis, she was suffering at the time of their onset from menopausal symptoms also.

The close relation between the glands of the endocrine system is stressed in medical literature at the present time: the onset of symptoms which might be attributed to simultaneous malfunction of the ovaries, the thyroid, and possibly of the pituitary could not be ignored when research is demonstrating how closely the functions of each of these glands are integrated. The justification for making such a diagnosis is further supported when the type and effect of the patient's therapy are examined.

Differential Diagnosis.

The age of the patient and the characteristic history of the onset of flushings, together with and following her last vaginal bleeding, indicates the onset of the menopause. The patient had noticed for two or three months that her monthly loss had been diminishing and its final complete cessation was to be expected. Some women pass through the menopause with very little disturbance of endocrine function; in such cases the monthly bleeding gradually diminishes until it finally ceases and there are no symptoms. In others there are menopausal symptoms of flushing, nervousness, irritability, and tachycardia which may last for a variable period and the origin of which appears to depend on the mental state of the individual and a disturbance of the endocrine control of the body. These symptoms may thus be caused by, or accompanied by, other systemic diseases such as hyperthyroidism, anaemia, diabetes mellitus/

mellitus or other disturbances of the physiology of the body. In such cases a careful examination and diagnosis are necessary in order to treat the factor which is causing the disturbance, since symptomatic treatment will be only palliative and may be harmful.

In this patient general systemic disease due to infection or neoplasm was eliminated by the history and examination. A year after the last menstrual bleeding the patient noticed the onset of symptoms suggestive of thyrotoxicosis. At this time her nervousness and irritability increased, she began to feel tired, a swelling appeared in her neck, and the incidence and severity of the flushings increased. Sleeplessness and loss of weight appeared, and until she was referred to the R.I.E. the symptoms and signs became more severe. She did not suffer from diarrhoea, or from any eye symptoms, and apparently did not feel abnormally hot or sweat more than normally. She suffered in February 1948 from breathlessness. This symptom was treated by the administration of iron, which apparently caused some improvement. As to whether this breathlessness was due to anaemia or to palpitations and some degree of heart failure it is difficult to decide. Since severe anaemia is uncommon in thyrotoxicosis, it was probably due to the latter. From a consideration of this history and of the findings on examination in the R.I.E. on 23.6.48, it may be concluded that the diagnosis of secondary thyrotoxicosis or thyrotoxicosis accompanied by cardio-vascular disturbance was justified. The absence of exophthalmos, of diarrhoea, and of sweating, together with the presence of symptoms suggestive of cardiac disease, and with a blood pressure at or above the higher limits of normal make the diagnosis of primary thyrotoxicosis unjustifiable. On clinical examination, both on 23.6.48 and when the patient was admitted to/
to/

to Ward 21, an adenomatous condition of the thyroid was found; such an enlarged nodular goitre is an outstanding feature of secondary thyrotoxicosis and also the occurrence of primary thyrotoxicosis becomes unusual in a patient of this age.

In spite of these symptoms and signs of secondary thyrotoxicosis it was probable that some of them might be of psycho-somatic origin. The most reliable method of differentiating an anxiety state from thyrotoxicosis is by examination of the sleeping pulse rate. In anxiety states it is normal even though the pulse rate is increased during the day. While the patient was in hospital, examination of the pulse suggests that there was a large nervous element in the production of her signs and symptoms. However, at this time her thyrotoxic clinical features had been controlled by thiouracil to a large extent and the strange surroundings of a hospital might well produce physical disturbances in a nervous patient. The long history, the positive clinical findings and the normal sleeping pulse make it probable that a condition of thyrotoxicosis had been present, but that by the time she was admitted to hospital the clinical features attributable to the raised metabolism had been controlled, and that these features were now the outcome of an anxiety state in a nervous patient, produced by the hospital surroundings and the knowledge that an operation might be necessary.

Progress.

After her condition had been diagnosed at the R.I.E., steps were taken to treat the thyrotoxic state from which she suffered. She still suffered from menopausal symptoms, but little notice can have been taken of them. The patient was put on a course of thiouracil, initially of 0.2 gm. thiouracil T.I.D., and after four weeks she was showing some improvement, both/

both subjectively and by an increase in weight. During this period the patient had been receiving a loading dose; after this the dose was reduced and a maintenance dose was given. Improvement continued to occur and was shown by further increase in weight, reduction of pulse-rate, and improvement of her nervous state. Such progress was to be expected with suitable doses of thiouracil. However, in October signs of over-dosage made themselves manifest in the appearance of swelling of the neck, with pressure symptoms, and of myxoedematous pouches under the eyes. It was because of these clinical features that the patient was admitted to the R.I.E.

Aetiology, Pathology, and Associated Endocrinology.

The pathology of thyrotoxicosis is closely bound up with the aetiology of the condition and with the state of the other glands in the body. Therefore the possible aetiology in this case will be discussed together with the pathology and associated endocrinology.

It has been stated that this is probably a condition of secondary thyrotoxicosis. If such is the case, the presence of a nodular goitre probably long preceded manifestations of hyperthyroidism (Cameron, 1947; Boyd, 1943). No history of such a condition could be obtained, no history of the patient having lived in a goitrogenic area could be obtained, and the family history is negative even though Bartels claimed to find a family predisposition in 60 per cent. of cases (Bartels, 1941, quoted by Cameron, 1947). How long the nodular condition has been present thus cannot be decided, but some suggestions can be made as to why in this particular case the thyrotoxic state arose.

Psychological or emotional disturbances are supposed to be responsible for the precipitation of a thyrotoxic state in the same/

same way that they may be one of the precipitating factors of a diabetic state (see Case III). It is probable that the person in whom such a disturbance will act must have a certain type of physical make-up which is already predisposed to the thyrotoxic state, possibly as a result of hereditary factors. This patient is of a worrying and nervous type and as a result is probably more likely to develop thyrotoxicosis than a more placid individual. Although no family history of the disease could be obtained, and the patient gave no history of any psychological disturbance, it is possible that her menopausal symptoms may have produced such a disturbance which was reflected in the production of symptoms by an already diseased thyroid.

The patient's last menstrual bleeding occurred in August 1946; it was followed by the menopausal symptom of flushing which, after nine months, had almost, but not quite disappeared. At the time of the menopause a large metabolic and endocrinal readjustment is necessary by the patient. Marine (1935) states that at the time of the menopause the body's requirement of iodine is increased and that at this time endemic goitre may occur. It is possible that in this patient circumstances may have been such as to produce a goitre during the readjustment associated with the menopause although, as stated above, it is probable that the goitre had been present for a longer period. Some factor, then, occurred which caused the goitre to take on toxic properties.

The clinical features of the menopause are produced by a gradual decrease and final disappearance of the ovarian hormones, in spite of the continued stimulation of the ovaries by the gonadotrophic hormones of the anterior pituitary. The secretion of the gonadotrophic hormones is controlled in part by/

by the ovarian hormones, since a diminished level of the latter hormones in the blood causes increased secretion of the former by the pituitary and vice versa. Not only does the pituitary control the activity of the ovaries but in the same way it controls the secretion of thyroxine by the thyroid with its thyrotrophic hormone. Both these pituitary hormones are proteins. Six such pituitary hormones have been separated, but Cameron states that "they may be breakdown products or modified products of a fewer number of compounds formed from these during the processes employed to separate them". Thus the gonadotrophic and thyrotrophic hormones may be part of the same large protein molecule, or at any rate, it is probable that their production by the anterior pituitary is closely related.

In this case a sequence of events probably occurred in which the pituitary, thyroid, and ovaries were involved. As a result of the decrease in the ovarian secretion at the menopause, the anterior pituitary became stimulated and larger quantities of its secretion were passed into the blood. It is possible that the menopausal symptom of flushing is due to this excessive release of pituitary hormone. Although this secretion had no effect on the ovaries, the already diseased thyroid responded to the release of excess pituitary hormone by increasing its hormonal output and thus the thyrotoxic condition was produced.

The effect of thiouracil therapy would be to exaggerate further the existing state of affairs. Thiouracil acts by interfering directly with the synthesis of thyroid hormone, probably by preventing the iodination of thyroxine. The lack of thyroid hormone thus produced results in a further stimulation of the anterior pituitary, with a resulting increase in its/

its secretion, particularly at this period of thyrotrophic hormone. Hyperplasia of the thyroid followed, although further thyroxine could not be produced. The symptoms of thyrotoxicosis before treatment were fairly severe, but in spite of this only a low maintenance dose of thiouracil was required and this brought the thyrotoxic symptoms under complete control. The ensuing enlargement of the thyroid can be explained by the already huge secretion of hormones from the anterior pituitary; only a slight increase in output of thyrotrophic hormone would be necessary to cause hyperplasia of the thyroid and this was produced by the thiouracil therapy.

On admission, the patient was found to have a much enlarged thyroid gland and to have few remaining signs of thyrotoxicosis. Examination of the heart showed it to be slightly enlarged. As a result of thiouracil therapy the features of thyrotoxicosis disappear gradually, the maximal improvement occurring at the end of two or three months. The tachycardia and high pulse pressure are generally the last signs to improve; thus cardiac enlargement also remains for a long time. Gain in weight occurs throughout treatment and provides the best way of gauging the patient's progress.

This patient was still under-weight and had an elevated pulse-rate and pulse pressure; her B.M.R. was also near the upper limit of normal, her reflexes were brisk and she had a slight tremor in her fingers. It is probable that these signs were principally the outcome of the patient's mental and nervous make-up, since if they were due to thyrotoxicosis the B.M.R. would have been abnormally high. In spite of these signs suggestive of thyrotoxicosis she had a myxoedematous facies and a lethargic appearance.

Thiouracil therapy had been employed for some time before admission/

admission, in fairly large doses. The aim of such therapy is to restore the patient's condition as closely as possible to normal. Normality in an out-patient is estimated by changes in weight and cardio-vascular signs. If excessive thiouracil is given, the thyroid hypertrophies and myxoedema may be produced. Therapy should be ^{so} controlled that neither of these states is produced. In this patient the former did occur and early slight signs of myxoedema were showing. Little reliance can be placed on the B.M.R. estimations in this patient, since their elevation was probably the outcome of an anxiety state, the thyrotoxic symptoms were well controlled, and it is thus obvious that prior to admission thiouracil had depressed the metabolism so far that a myxoedematous state was threatening.

In order better to estimate her condition while in hospital as many quantitative measurements were made as possible. Improvement was shown by the increase in weight, diminishing circumference of her neck and fall in blood pressure and pulse rate. The patient's abnormally low weight for her size, and enlarged heart, showed that she was still recovering from her illness. Falls in the pulse-rate and blood-pressure occurred and reflected an improvement in her general condition, although these observations were indicative of psychological improvement rather than any sudden change in her physical condition. The diminishing circumference of her neck showed a return towards normal endocrine balance.

An attempt was made to estimate the state of the patient's metabolism by the method of Bene (Lancet, 1949). This was done partly in order to test the efficacy of the method since it could be checked by measurements of the B.M.R. The latter was of value in this patient only in that it indicated the metabolism was not grossly raised, and thus was of some help in/

in differentiating between a thyrotoxic and anxiety state. The R.P. index varied from hyper-normal to sub-normal values while the patient was in hospital. In general, it indicated that the metabolism was approximately normal, but it appears that little reliance can be placed on its variations in a case where the metabolism is probably close to normal since R.P. index was highest when the patient was admitted and the metabolism might be expected to be lowest, and was least on discharge when metabolism would be expected to be highest as a result of remission of thiouracil therapy.

Treatment.

Treatment consisted of a period of rest and sedation followed by drug therapy. It is noteworthy to what a large extent her condition improved by sedating the patient and keeping her in bed, and supports the conclusion that her symptoms had a large psychological basis. This improvement is to be attributed not only to the rest but also to the discontinuance of thiouracil therapy. As a result of the latter, the output of thyrotrophic hormone by the pituitary was decreased and some atrophy of the thyroid occurred. During this treatment, also, her menopausal symptoms diminished.

As a result of prolonged thiouracil therapy thyrotoxicosis can often be cured. In this case the thyrotoxic condition was controlled, but had not disappeared. So far the treatment in hospital had been of a temporary nature in order to observe the patient and decide what measures could be used in order further to alleviate her condition.

The endocrinological basis of her subsequent drug treatment has already been discussed. Dienoestrol was given to diminish the secretion of the pituitary hormone and thus help to control the menopausal symptoms, and thiouracil was given to control/

control the thyrotoxic condition. It was hoped that the dienoestrol would also have the effect of lessening the pituitary stimulation of the thyroid and thus prevent thyroid enlargement and pressure symptoms. Only a small maintenance dose of thiouracil was found to be necessary.

Subsequent progress showed maintenance of the improvement. The patient felt, and clinically was better on 14.1.49, when taking 0.05 gm. thiouracil and dienoestrol 0.6 mgm., daily, than on 26.8.48, when she was taking 0.2 gm. thiouracil daily. On the former date, also, her menopausal symptoms had disappeared, whereas on the latter they were causing her discomfort.

On 15.2.49 she reported that she had been suffering from the effects of the oestrogen therapy on her uterus, but they were not considered to be severe enough to reduce her dose of dienoestrol. On the last date on which the patient was seen, her thyrotoxic features were slight. Her blood pressure was almost normal, only a slight tachycardia was present, and her weight was steadily increasing. Her neck was still enlarged, due presumably to the continued stimulation by the pituitary hormone, although it was not as large as when she was admitted to Ward 21. Its rapid variations in size must vary with changes in her general metabolism. Were it possible to vary her drug therapy in consonance with these variations in metabolism, such changes in the size of her gland could be eliminated. An alternative explanation of these variations in size may be that they are due to haemorrhage into the nodular areas; however, if this were so, the gland would be hard, not soft.

Surgical treatment is often indicated in patients with secondary thyrotoxicosis with large adenomas. In this patient surgical/

surgical treatment is contra-indicated until the effects of the present treatment can be observed. It is very probable that if the patient can be tided over the period during which pituitary and menopausal symptoms are present, the thyrotoxicosis will ultimately become less pronounced about the same time as, or shortly after, the oestrogen therapy can be dispensed with. Alternatively, prolonged thiouracil therapy may result in exhaustion of the thyroid gland, with disappearance of the symptoms. Should neither of these possibilities occur, and should the thyroid continue to fluctuate in size and symptoms of thyrotoxicosis continue to occur in spite of effective medical treatment, the question of surgery would have to be considered seriously.

Conclusion.

This case demonstrates the marked inter-relation of the glands of the endocrine system and shows how advantage may be taken of this in treatment. It shows how important it is to make a thorough investigation of the patient for all the signs of endocrine disturbance and how, if some are missed, treatment may result in continuance of the initial symptoms and inability to find a method of treatment which will satisfactorily control the condition. As more notice is taken of all the clinical features which a patient may show, no matter how trifling, so by their successful treatment will the patient's physiology be brought more and more to resemble the normal. In this case the sudden withdrawal of ovarian secretion at the menopause precipitated a condition which could only be treated by restoring the status quo. Provided that medical treatment can restore the physiological condition of the patient to normal over a long enough period, it is probable that a gradual return of the patient's endocrine system to normal will occur and treatment by/

by drugs will become less and less necessary.

In all endocrine disturbances there is supposed to be a general glandular upset but it is rarely that the nature of this upset can be determined as clearly as it was in this case, and it is still more rarely that poly-glandular therapy can be instituted with an artificial adjustment of the endocrine system so that a condition almost of normality is produced. Other cases in this series show evidence of a poly-glandular disturbance, but poly-glandular therapy was not possible. The relation of this case to the other cases showing endocrine dysfunction will be considered later.

CASE III

PROFESSOR D. M. LYON

Mr. C. BRYHAM OLIVER

Ward 21,

Royal Infirmary
of Edinburgh.

DIAGNOSIS: DIABETES MELLITUS WITH NERVOUS
AND OTHER COMPLICATIONS.

C. BRYHAM OLIVER

aet. 62 Married
4 children.

21 Balfour Street,
North Berwick.

Occupation: Unemployed, formerly public speaker.

Doctor: Dr. Donald,
St. Helen's
North Berwick.

Date of Admission: 12.4.48.

Date of Examination: 15.4.48.

Date of Discharge: 29.5.48.

Complaint: Swelling of legs and feet for three years,
painful ulcers on left foot for five years.

HISTORY

History of Present Illness:

The patient was engaged in strenuous political activities at the beginning of 1935 which, in March, culminated in a marked difference of opinion with his superiors and fellow-workers: as a result the patient was forced to resign from his position in the political party which he supported. During this period he was subjected to considerable nervous distress and worry, and he attributes his symptoms and following illness to the occurrences during this period.

In March 1935 the patient weighed 17 stone 2 lbs. but soon after this he noticed that his weight had begun to fall and continued to fall steadily till the end of the year. In June he observed that he was beginning to feel abnormally thirsty and to pass excessive quantities of urine. He found that he had to get up to urinate at night and during the latter part of the year he had to rise three or four times each night and was unable to hold his urine for more than two hours during the day.

Following the resignation from his political party he

he began to write and read more than previously and also began to take up walking for pleasure to a greater extent, although he had always done this to some degree. He found that as the year proceeded, and in spite of the fact that he had been having a good summer holiday, the walking became more difficult because he felt tired, and less willing to undertake long walks. The tiredness became more marked and the patient preferred to lie down in a chair although he did not feel sleepy. He found however that a rest did not improve his tiredness and at the end of a rest he felt just as fatigued as before it.

Before the onset of his illness the patient had occasionally suffered from slight and infrequent attacks of cramp in his legs. During the later months of 1935 the patient began to have attacks of cramp at night in bed which woke him up. The pain was severe and his muscles passed into spasm and felt very lumpy. If he massaged the affected muscles the condition improved and he could go to sleep again. Such attacks lasted for 15-30 minutes. The cramp occurred more frequently as he became more ill until finally he became afraid of going to bed. At the end of the year the cramp began to occur during the day as well as at night. His legs became stiff and he became unable to move them, at the same time they also felt numb and dead. Such attacks occurred particularly when the patient was walking or climbing stairs and they became more severe and frequent as the disease progressed until they occurred as often as once or twice a day.

In spite of his physical tiredness the patient felt alert mentally. Up to 1935 his eyesight both for distant and near vision had been excellent. In the middle of the year he noticed that his sight was rapidly deteriorating and finally he had to get glasses for near vision; his distant vision became worse but glasses did not become necessary.

necessary.

At the end of the year he went to consult his doctor who after treating him for a short time on a diet sent him to the R. I. E. where he was placed in Ward 23. He was immediately given insulin - soluble. Rapid improvement occurred, first in distant vision, to such an extent that vision which before had been hazy across a street now became exact and almost as good as it ever had been. Improvement in near vision also occurred so that it became possible again to read small print although glasses could not be dispensed with. The latter improvement occurred more slowly than the improvement in distant vision. The thirst and polyuria disappeared completely. The tiredness improved gradually, and completely disappeared from the trunk and upper limbs but his lower limbs did not recover to the same extent and the symptoms of stiffness and inability to stretch the legs easily and freely, although improved, have never disappeared completely. The cramp disappeared completely and he has not suffered from it since. The patient was discharged in March 1936 greatly improved, on a stabilizing dose of Zinc Protamine Insulin and on a diet.

The patient remained well till 1940-1 when he began to notice that his feet were not healthy. His toes on both feet began to develop sores which refused to heal. These sores developed on previous small injuries or appeared spontaneously. They developed into small ulcers and either took a long time to heal or did not do so. Scratches and cuts on the legs and elsewhere on the body still continued to heal quite normally. His walking became slower and his range became restricted principally due to weakness in his legs which was becoming more marked. His style of walking remained the same and he did not trip or take shorter or higher steps. At this time and during the following years he consulted both his own

own doctor and the R. I. E. several times for treatment for the ulcers, which were treated by dry dressings applied locally and by rest, also his insulin was changed to globin insulin.

In January 1946 the patient slipped on the ice and fractured the neck of his left femur. He was admitted to the R. I. E., the fracture was manipulated and put in plaster. The fracture healed satisfactorily but the leg remained $1\frac{1}{2}$ inches shorter than its fellow and there was some residual stiffness in the hip, knee, and ankle joints which necessitated his walking with a stiff leg. The ulcer which he had on the left foot at this time was treated but did not heal up. On discharge it caused him no pain and its condition did not change, although if he walked too much (i.e. much more than three-quarters of a mile) the foot became swollen and the ulcerated area became tender and deep pain was felt.

After the fracture had healed the patient again became unwell in the latter part of 1946. An acute attack of swelling occurred which involved his whole body including his face and arms and trunk as well as his legs. The patient had felt unwell before the attack occurred; he suffered from malaise, tiredness and on the day of the attack he felt feverish and had to put off a dinner-party for which he had come to Edinburgh, in order to return home to bed. The swelling was severe and extensive and the patient's doctor prescribed digoxin and ordered the patient to remain in bed. The swelling rapidly disappeared and after staying in bed for a week the patient resumed his normal activity. His doctor made him go on taking digoxin, 0.75 mgm. daily, four times a week although the patient was unwilling to do so. Previous to this attack of swelling the patient had suffered from minor attacks of breathlessness, which principally occurred after he had been talking very much but which also tended to occur when his

his feet troubled him or became swollen. He had noticed the onset of this breathlessness particularly in 1945, but it was not sufficiently severe to cause limitation of his activities any more than did his ulcerated foot.

Swelling continued to occur in the patient's legs but he found that this could be prevented by taking digoxin although he also discovered that remission of the drug for over three weeks was necessary before the swelling in his legs became serious. As a result he omitted to take the digoxin for periods of a month or more over the next year and a half and would only start taking it again when the swelling inconvenienced him. Attacks of breathlessness often occurred when his feet became swollen or when he was over active but they also cleared up when he took digoxin. This breathlessness has persisted to a varying degree up till his present admission to hospital.

The patient tests his urine for sugar and he has noticed that whenever any swelling occurs sugar appears in increased quantities and he has had to increase his dose of insulin.

In February 1948 the ulcer on his left foot broke down and became deeper, and the swelling which previously had been confined to his feet when walking now extended up to the knees in both legs and was present all the time. The patient went to bed and called in his doctor. He was told to remain in bed and his dose of insulin was trebled so that he was taking 60 units of soluble insulin daily and this level has had to be maintained ever since. His legs slowly began to improve but he now became very breathless whenever he had to get out of bed to pass urine and after returning to bed he lay panting for half an hour or more. Although this breathlessness also began to improve after he had been in bed for two or three weeks his doctor referred the patient to the R. I. E. and he was admitted on 12.4.48. to Ward 23 and was transferred to

to Ward 21 on 21.4.48.

It is only since the patient has had diabetes that ulceration of his feet has occurred. The swelling in his legs which latterly has been associated with some breathlessness also has been becoming worse in the last two or three years - since he has developed diabetes. He says he has not taken any digoxin for about the last nine months. He has had no symptoms suggestive of intermittent claudication and has had no pain in the chest suggestive of angina pectoris. He has had stiffness in his left leg since the fracture but recently it has seemed to be getting less severe. Occassionally after a long walk he has had some pain in his left knee. He has no difficulty in passing his urine and his bowels function normally and regularly.

Summary of the Patient's Illnesses

1916 Malaria

1917 Varicose veins and ulcers

1932 Bronchial Asthma. This began suddenly during the winter and recurred each winter up to 1935; since then although it still ~~recurs~~ its severity has been diminishing. It was associated with dry sharp fits of coughing and very considerable breathlessness.

1935 Diabetes Mellitus. Since the occurrence of diabetes the patient has had a long history and has been admitted to hospital several times.

1940 Sepsis in left foot

1945 Breathlessness and oedema in legs

1946 Fractured femur

1948 Sepsis in left foot and swelling of legs.

Social History

The patient is at present retired and living a peaceful existence at North Berwick. There he takes a very short walk most days to see some local friends, writes and reads and lives

lives with his wife and children. He takes an intelligent interest in the state of his health, testing his urine about 2 - 3 times a month and if any fresh symptoms occur or if he is feeling unwell, he consults his doctor. He keeps to his diet fairly closely, and understands the method of adjusting his insulin dosage, increasing it whenever he has an exacerbation of his ulcers. He has had insulin reactions, and whenever he gets one immediately takes some sugar. During such reactions he has no changes in his vision. Before developing diabetes he used to smoke cigarettes and a pipe; he was a heavy smoker. Since developing diabetes he has smoked about one cigarette a day. He takes no spirits and only very occasionally a little beer.

Family History

Patient married : wife well.

Four children:

three girls - all married.

one boy aged 25 : well.

Mother died aged about 60 years; she had suffered from asthma all her life.

Father died 65 years from a gastric condition, possibly cancer of the stomach.

The patient has one brother and three sisters. One sister and the brother are alive and well; one of the other sisters suffers from frequent and severe headaches, and the third sister is a chronic invalid.

There are no relations with diabetes or with a history of heart failure.

PHYSICAL EXAMINATION

General Inspection

A healthy looking slightly bald white-haired man. He is not pale or cyanosed though his ears are deep red in colour. His face is somewhat gaunt and his malar bones can be easily

easily seen. He is sitting up in bed propped up by several pillows and is slightly breathless. There is no finger clubbing but Heberden's nodes are present on his fingers and his inter-phalangeal joints are swollen. There is a cage over his feet.

Temperature: 98.6° F

Actual weight: 11 stone 8 lbs.

Ideal weight: 15 stone 10 lbs.

Height : 6 foot 5½ inches.

Cardio-vascular System

Pulse :

Radial Pulse: Normal rhythm. Volume regular and normal. The pulse wave is normal and of constant force. Vessel wall impalpable.

Rate: 88/minute

Blood Pressure: 180/100

Brachial Pulses: Pulsation could be seen along the whole length of each upper arm between and through the muscles.

Femoral Pulses: Strong and equal. Artery walls hard and irregular.

Popliteal Pulses: Strong and equal.

Dorsalis Pedis: Both palpable, weaker than the proximal pulses.

Posterior Tibial Pulses: Palpable, weak.

Precordium:

There is no pulsation or venous congestion in the neck. The apex beat is just visible, there are no other pulsations in the chest.

The apex beat is diffuse and is felt in the 6th inter-costal space, 3 inches from the mid-line. There are no thrills.

On percussion the area of cardiac dullness is found to be diminished.

diminished;

the right border of the heart is opposite the right para-sternal line.

the left border

in the 6th inter-costal space is 3 inches from the mid-line.

" " 5th " " " "2½ " " " " .

" " 4th " " " " 2 " " " " .

superior to the 4th space it is opposite the left para-sternal line.

On auscultation the heart sounds are closed and pure.

Venous System:

There is no sacral oedema.

There is no ankle oedema.

Varicose veins cannot be seen in the lower limbs when the patient is lying down, but when he stands up they appear in the calf of each leg and on the medial surfaces of the thighs. The long and short saphenous systems are involved on each side.

Fundus Oculi:

There is no marked tortuosity of the vessels or kinking of the veins where the arteries cross them. No retinal haemorrhages or exudates can be seen. The optic discs are grey and their margins cannot clearly be defined. The macular regions and peripheries of the fundi are normal.

Respiratory System

The chest is deep antero-posteriorly and the sternum projects forward. There is some splaying of the lower ribs on each side, and a groove passes back on each side below the nipple. Posteriorly some kyphosis is present over the upper thoracic vertebrae and there is a slight right scoliosis of the lower thoracic vertebrae.

The chest moves slightly upwards and forwards on respiration and there is marked movement of the abdomen. The

The patient is sitting up in bed and pants slightly when he moves; he is not cyanosed at all. The sterno-mastoids and other accessory muscles are used slightly.

Respiration Rate: 20/minute

Chest Expansion: 2 inches.

Chest expansion is equal on both sides. No friction felt. The chest is hyper-resonant in all areas. The breath-sounds are broncho-vesicular in all areas. High pitched rhonci are present anteriorly in the right lung. Vocal resonance is equal and slightly diminished in all areas.

Central Nervous System

Mental State:

An alert and fairly intelligent man.

Cranial Nerves:

The patient requires glasses for near vision. Distant vision is good.

The pupils are normal and react normally to light and accommodation. Nothing abnormal detected in the cranial nerves.

Spinal Motor Nerves:

Muscle power in the upper limbs are normal. In the left lower limb the power is diminished in the quadriceps femoris. The other muscle groups are equal in each limb.

There is some wasting present in all muscles.

Tone normal : no tremor or spasm.

Spinal Sensory Nerves:

No diminution or loss of sensation in the upper limbs or trunk.

In the lower limbs:

Sense of pain is lost over the distal half of the plantar aspect of the feet and plantar aspects of the toes, and also over the lateral half inches of the medial and lateral margins of the distal halves of the dorsal aspects of both feet.

feet.

Sense of light touch. Sense of touch to wool is absent in both limbs over the whole foot except for a small area of the dorsal surface between the malleoli extending forwards to the roots of the toes, and over the lower halves of both legs the area of loss extends on the medial sides to just above a point half way between the knee-joint and the malleolus and on the lateral side to a point about two inches below this.

Vibration sense. Absent over both malleoli, the tibial shafts, and patellae in each limb.

Joint sense. Much diminished in the phalangeal and metacarpo-phalangeal joints. Passive movements of the toes are not distinguished and mistakes are made in knowing which toes were moved.

Tendon Pressure sense. Absent in the Achilles tendon in the right limb and diminished in the left limb. Deep pressure pain is absent in the toe webs.

Reflexes:

The conjunctival, palatal and abdominal reflexes are normal. The plantar responses are flexor.

Deep reflexes:

Upper limbs		
	Right	left
Biceps	+	+
Brachio-radialis	+	-
Triceps	+	+
Lower limbs		
Knee	+	+
Ankle	-	-

Trophic changes:

An ulcer 6 m.m. in diameter is situated over the head of the fifth metatarsal bone on the plantar surface of the

the left foot. The wall of the ulcer is sloping, it is mobile on the subcutaneous tissues and is tender to touch. The skin is thickened and darkened distal to the ulcer and at the bases of the fourth and fifth toes. Thick yellow pus is present on the dressing. Some crepitation is detected on palpating the surrounding skin which is thickened and in the process of peeling. Other ulcer scars are present on the plantar aspects of both feet but are soundly healed. Brown mottled discolouration and some scarring is present on the medial and posterior surfaces of both legs with some peeling of the skin. This is more marked on the right leg.

Urinary System

Kidneys impalpable

Bladder impalpable

Urine:

Colour - yellow

Specific gravity - 1022

Reaction - Acid

Abnormal constituents

Sugar: +

Acetone: -

Albumen: -

Blood: -

Alimentary System

Mouth:

Teeth: false but well fitting.

Tongue: clean and moist; papillae normal.

Mucous membrane and tonsils: normal.

Abdomen:

Liver and spleen impalpable. No herniae.

Nothing abnormal detected.

Locomotor System

The left leg is shorter than the right leg by $1\frac{1}{2}$

1½ inches. The shortening is confined entirely to the femur; the distance between the adductor tubercle and medial malleolus being the same in each leg. There is no limitation of movement at the hip-joints but flexion of the left knee-joint is slightly limited. There is palpable crepitation in the knee-joint when it is moved.

Ankle-joints: nothing abnormal detected.

Skin and Subcutaneous Tissues

The skin is soft healthy and elastic except in the areas where there are trophic lesions.

In the legs and feet the skin is equally warm on both sides and is pale in colour.

There is loss of subcutaneous tissue over the whole body, this is particularly noticeable in the limbs, which are very thin.

Endocrine System

Nothing abnormal detected.

No enlarged lymph glands detected.

Examination of the Blood

Red Blood cell count: 4,500,000/cubic m.m.

White Blood cell count: 7,800/cubic m.m.

Hæmoglobin : 70%

Special Examinations

24.4.48 X - ray Report.

Chest: A - P Film

There is emphysema with associated chronic bronchitic changes and some fibrosis. In the left apical zone there is fibrotic infiltration with small areas of calcification. These were recorded in 1940 and presumably represent old healed Tuberculosis. There is a degree of cardiac enlargement and the hilar shadows are prominent.

27.4.48 Bacteriological Report.

Swab of pus from ulcer of foot. Some pus cells;

cells; some cocci present, shown by culture to be staphylococcus albus with a few Haemolytic Streptococci.

Biochemistry Reports

13.4.48 Blood sugar : 78 mgm %
14.4.48 Fasting Blood sugar: 160 mgm %
27.4.48 Fasting Blood sugar: 283 mgm %
Fasting urine sugar: 3.7 gm. %
5.2.49 CO₂ combining Power: 70 vols. %
Blood Cholest^erol : 266 mgm. %

Plasma Proteins

Albumen : 3.72 gm. %
Globulin : 2.23 gm. %
Non Protein Nitrogen: 41 mgm %
Blood Urea Nitrogen: 17 mgm %
Vol. urine for one hour: 58 cc
Urine Urea Nitrogen : 944 mgm %

Urea Clearance: 101 % of normal.

While the patient was in the R. I. E. the volume and specific gravity of a 24 - hour specimen of urine were measured periodically in order to get an estimate of the patient's kidney function.

<u>Date</u>	<u>Volume</u>	<u>Specific gravity</u>
22.4.48	1260 cc	1022
25.4.48	2160	1030
29.4.48	1770	1024
3.5.48	2880	1024
6.5.48	2220	1026
10.5.28	1200	1014
14.5.48	2880	1012
17.5.48	2700	1019
21.5.48	2520	1015
24.5.48	1200	1004

TREATMENT

TREATMENT

Treatment was directed toward

- (1) Improvement of the ulcer on the patient's foot.
- (2) Stabilisation of his diabetic condition by diet and Insulin.

- (1) The ulcer was treated:

by local measures. These included complete rest in bed and protection of the ulcerated area by a cage over the patient's legs and local dry dressings which were changed twice daily. On 23.4.48 the sole was incised the abscess was opened and the pus released. On 11.5.48 massage and exercises were commenced to improve the condition of the patient's muscles and circulation to the trophic areas.

By general measures.

22.4.48 - 29.5.48 Benerva 25 mgm B.I.D.

23.4.48 - 27.4.48 Sulphadiazine 1 gm 4 hourly.
up to a total of 25 gms.

28.4.48 - 6.5.48 Penicillin 100,000 units B.I.D.
up to a total of 1,600,000 units.

The patient tended to suffer from constipation and he was accordingly given Liquid Paraffin $\frac{1}{2}$ fl. oz. daily from 17.5.48 till his discharge .

- (2) The diabetes was controlled by prescribing a diet containing

Carbohydrate	160 gm.
Protein	102 gm.
Fat	145 gm.
Calories	2380

A dose of Zinc Protamine Insulin was given daily at mid-day varying from 30-40 units. The dose was adjusted so that sugar should just be absent from the morning, mid-day and evening samples of urine. On 28.4.48 and 29.4.48 10 units soluble insulin was also given at mid-day since at this time the patient was having some digestive disturbance

disturbance and it was found difficult to control the associated fluctuation in blood sugar. As the patient's septic condition improved it became possible to reduce the requirements of insulin so that at the time of discharge he only required 30 units Zinc Protamine Insulin daily.

29.5.48 Discharged.

The patient was given a diet containing

Carbohydrate 175 gm.

Calories 2500

He was discharged on a dose of 30 units Zinc Protamine Insulin daily.

He was instructed to get a special bar fitted to the soles of his shoes so that the callous area on his foot would be protected when he walked.

PROGRESS

The patient's progress was measured by reference to

- (1) The condition of his foot.
- (2) His breathlessness and general condition.
- (3) The control and stabilization of his diabetes.

21.4.48 Rest and conservative treatment have resulted in softening of the hardened and necrotic skin round the ulcer, and the skin is beginning to peel away. The ulcer is not painful but it is tender to touch.

The patient has become much less breathless and now reads lying down in bed and although he still gets breathless if he moves about much there is a great improvement.

23.4.48 The ulcer and abscess on the foot was opened and some yellow pus was released. The wound was left open and a dry dressing applied.

27.4.48. The results of the blood and urine sugar estimations made it necessary to give soluble insulin, 10 units as well as the zinc protamine insulin in an attempt to control the blood sugar level, on 28 and 29.4.48. On

On 30.4.48 the urine sugar loss again returned to a trace on Zinc Protamine Insulin alone and so the soluble insulin was discontinued. During this period the daily dose of Zinc Protamine Insulin was 36-40 units.

2.5.48 The patient has been suffering from spasmodic abdominal pain, indigestion and the passage of flatus. Loss of appetite, nausea and constipation have also been present. These symptoms were attributed to the effect of the sulphadiazine and were treated by cream of magnesia, charcoal and kaolin biscuits.

8.5.48 The necrotic skin on the sole of the foot has peeled away leaving a large area about 2 cms. in diameter covered with healthy granulation tissue. The infection has subsided.

The patient looks well and no longer suffers from any degree of breathlessness. His appetite has improved and the alimentary symptoms have disappeared.

Examination of his urine shows that the diabetes is being kept well under control.

15.5.48 The granulating area is getting smaller and healing well. The patient is feeling well and the massage and exercises are proving of benefit to the patient's recovery.

28.5.48 The wound is covered with skin and well-healed. The area where the ulcer was is marked by a scar. The patient's general condition shows a great improvement. He is no longer breathless when he walks about and no swelling of his feet or ankles has occurred when he has been up.

His diabetes is controlled well on a diet and 30 units of Zinc Protamine Insulin daily and his urine only shows a trace of sugar in the morning specimen.

29.5.48 Discharged.

Subsequent Progress

Subsequent Progress

5.2.49 The patient was asked to report to the ward in order that certain biochemical examinations might be done, and an opportunity was taken to examine him clinically.

The ulcer on the sole of his left foot has reappeared. It is in the same place as when he was in Ward 21 but is much smaller. There is a little pus on the dressing. It is not painful and the bar on his shoe protects his sole and the ulcer causes him very little discomfort when standing or walking. The patient is feeling well and is leading an active life during which he takes part in discussions and addresses large meetings. He gets breathless when he is over-active but he can walk for $\frac{3}{4}$ mile easily and climbed North Berwick Law at Christmas. There is some swelling of his feet which extends to just above his ankles. His liver is not palpable. He has had no severe asthmatic attacks or colds.

He is taking his diet and 36 units of Zinc Protamine Insulin each day. He says his urine shows very little sugar.

DISCUSSION.

This patient gives a history extending back for over thirty years, during which he has suffered from numerous conditions, some of which have been of a chronic nature and are still active, and others of which have been acute and successfully and completely dealt with by treatment.

The varicose veins, asthma, diabetes and osteo-arthritis in the left leg are the principal chronic conditions from which the patient is suffering and are the conditions which have produced the clinical features necessitating such frequent medical attention.

The diagnosis of the diabetes is confirmed by clinical examination, and the patient's response to therapy. The differential diagnosis of the pulmonary condition and the relation which it bears to the cardio-vascular system will be discussed under Pathology as will the condition of the varicose veins and the oedema from which the patient suffers.

Aetiology.

The history, clinical and laboratory examinations show that the patient has suffered from asthma and a bacterial affection of the lungs. The patient's mother had asthma and one of the patient's sisters suffers from frequent and severe headaches, possibly of a migrainous character. Migraine appears to bear some relation to asthma, and heredity exerts a strong influence on the occurrence of both conditions. Asthma occurs more commonly in boys and migraine in girls born of parents who suffer from one of these conditions. This has occurred in this particular family and, even though the patient only developed asthma in 1932, he probably had a constitutional diathesis to the development of asthma, which appeared at this date/

date in response to some precipitating external factor. The fibrosis and features of an inflammatory condition in the lungs may have been responsible for the development of the asthma or may have developed in lungs, the resistance of which had been decreased by the asthma. Since some calcification and fibrosis had been recorded in 1940, the former supposition is probably the more correct.

The development of varicose veins and ulcers in 1917, when the patient was 31 years old, is somewhat early. The occurrence of varicose veins may be influenced by heredity (Beattie and Dickson), the predisposing cause being a congenital or inherited weakness of the walls and valves of the veins. Mechanical increase in the blood pressure within the veins, caused by obstruction to the return of the blood by emphysema or cardiac failure, or by gravity in the legs of people whose occupation entails much standing, is an important cause of varicose veins. In this patient the history of pulmonary disease did not appear till long after the development of the varices and the history of heart failure only appeared later still. It is possible that in this patient there was a weakness of the walls of the veins and that the patient's active life of political rhetoric would throw a greater strain on these veins than is usual, with their resultant degeneration and dilatation at this time in the patient's life.

The clinical features at the onset of the diabetes were typical of this disease and because of the long period with inadequate treatment they became greatly exaggerated. In his Banting Memorial Lecture in 1948 Professor Young (1948) suggests that the cause of diabetes is not wholly bound up with deficiency of pancreatic secretion as was believed in the past, but that it consists of a syndrome which experimental evidence shows may be associated with pituitary as well as pancreatic dysfunction./

dysfunction. In experimental animals, injection of the diabetogenic anterior pituitary extract will produce diabetes. The clinical application of this discovery to the disease in human beings is not known, but at least it would seem that the pituitary may play some part in the production of the condition. These observations are of interest in considering the onset of the disease in this patient. The patient is abnormally tall, and at one time, before the onset of the diabetes, was correspondingly heavy. Such abnormal growth is controlled by the endocrine system in the body and more particularly by the growth hormone of the anterior pituitary. For the patient to grow as he has done there must at the time of puberty have been some abnormal secretion of the anterior pituitary.

The control of the emotions is now relegated to the hypothalamus, which also plays some part in controlling the secretory activity of the pituitary and the carbohydrate metabolism of the body (Best and Taylor, 1945). In 1935 the patient went through a period of intense nervous worry and strain which would result in increased activity of his cerebral cortex and emotional centres. Such hypothalamic activity might well be reflected in abnormal control of the pituitary and disturbance of carbohydrate metabolism of the body, particularly when it is remembered that the pituitary had already had a period of abnormal secretion. Thus it may well be assumed that the pituitary has played some part in causing the onset of the diabetes in this case. This is supported by reference to the onset and course of the disease.

When the disease appeared, the patient was 49, he was not over-weight for his size and active life and it could not be maintained that the disease was caused by obesity. In its severity the disease resembles the diabetes of adolescence, when/

when a general endocrine readjustment is occurring. The relatively late age of onset, in the absence of any other disorder, but in the presence of the psychological strain and previous pituitary disturbance, coupled with the severity of the condition, support the conclusion that the pituitary may be involved.

Pathology.

It is difficult to decide how much of the pathological change in the chest can be attributed to inflammatory conditions and how much to the asthma, but some assessment must be made of the degree of interference with the pulmonary circulation. The fact that fibrosis and calcification were found in the left apical zone in 1940 makes it probable that the pathological changes here have been present for some time. These lesions may be the remains of a severe primary tuberculous infection, in which case they would be very old.

The emphysema, found radiologically, was confirmed by clinical examination. An enlarged heart was to be expected with such a history, and the fact that it was diminished on clinical examination was due to the emphysematous lungs encroaching on the area of cardiac dullness. The finding of rhonchi indicated the presence of swelling of the mucous membrane or of a thick, sticky secretion in the bronchi, both of which accompany inflammatory changes in the bronchi. These inflammatory changes have resulted in some degree of pulmonary fibrosis. They also must have been present for some time, although the bronchitis probably followed the onset of the asthma since bacterial invasion would be easier in a lung weakened by emphysema and deficient blood-supply.

It was not until 1946 that signs of cardiac failure began to appear. Nephritis would have produced similar symptoms to the/

the "acute attack of swelling", malaise and fever. However, the absence of any urinary changes and the response to digitalis therapy, together with the antecedent history of asthma, must have convinced his doctor that the diagnosis of right-sided cardiac insufficiency was correct. The excellent renal function tests make it unlikely that the patient has ever suffered from a severe attack of nephritis. The malaise and fever associated with the oedema were probably due to an exacerbation of the bronchitis. The dyspnoea from which the patient has since suffered is probably primarily of respiratory origin although a deficient circulation probably contributes to it and is responsible for the right-sided cardiac insufficiency, i.e. mild cor pulmonale which clinically is demonstrated by the patient's swollen lower limbs.

A mild essential hypertension is present. It is not sufficiently high to cause cardiac signs per se. There is no sign of congestive failure and there is no history to suggest that the heart is de-compensating in the presence of a raised diastolic pressure or that there has been any lesion in the myocardium. There is no family history of hypertension. Although there may be some vascular changes in the lower limbs, the ulcer is a trophic, not a gangrenous condition. The absence of any renal insufficiency shows that the renal blood-supply is still good, and examination of the fundi demonstrate no arterial changes. The hypertension has probably arisen as a result of a constitutional diathesis. The diabetes may have hastened its onset but it is improbable that the hyperglycaemia has been present sufficiently long to have caused the arterial degeneration. The relation of vascular degeneration and diabetes is discussed more fully in the Summary.

Even though the appearance of the varicose veins long preceded/

preceded the cardiac insufficiency, the latter has probably increased their severity. It is possible that the varicose veins might be the whole cause of the oedema of the legs though, if that were the case, the patient would have complained of it sooner than 1946 and it would have been more severe when the patient had varicose ulcers in 1917. It is more likely that the varicose veins and the cardiac insufficiency both contribute to the swelling and that the veins make what normally would be only a slight degree of swelling much more severe. This is supported by the absence of any liver enlargement in the presence of fairly marked swelling of the feet.

Although the ulcer on the foot is not in the typical varicose ulcer site, and the typical varicose ulcers are well healed, the varicose veins are a contributory feature to the ulcers of the feet. By lessening the resistance of an already insensitive skin, they must predispose to its ulceration.

Osteo-arthritic changes are present in the hands. Similar changes are present in the left knee and must be the result of the fracture of the femur and consequent shortening of the left leg. The patient was a heavy man before the onset of the diabetes, but not abnormally heavy for his size. But the strain of this weight on an abnormal joint would hasten the onset of osteo-arthritis. By causing abnormal weight-bearing, the fracture may also be a contributory feature in producing the ulcer on the left foot.

The diabetes was present for almost a year before it was effectively treated. The longer the condition is left untreated, the more severe do the symptoms become and also the more impaired does the carbohydrate tolerance become (Cameron, p. 152); thus the severity of the symptoms and of the ultimate diabetic condition would have been averted if treatment had been carried/

carried out earlier.

The loss of weight, tiredness, thirst and polyuria are all produced as a result of the disturbed carbohydrate metabolism. The disturbances of vision are due to the changing refraction of the media of the eye caused by varying sugar and water content. When the diabetes was controlled, the patient's visual symptoms almost disappeared, although some permanent damage must have occurred since the patient has never been able to dispense with glasses for near vision.

The muscle cramp so characteristic of severe diabetes is attributed to dehydration of the tissues. The muscle cramp consists of a painful spasm of the muscles in the calves of the legs, although it may occur in the thighs or in the feet. The pain very closely resembles the pain produced when muscle works in ischaemic conditions. The application of a beaumanometer cuff, occluding the arterial supply, to the leg of a diabetic who has suffered from such pain, produces pain identical to that occurring in diabetic cramp when he moves his foot. The only difference is that the pain is unaccompanied by muscle spasm. Since the pain is so similar, it seems possible that it might be produced by a process similar to that producing ischaemic muscle pain. The "P" Factor of Lewis is supposed to consist of tissue metabolites produced as a result of muscular contraction under ischaemic conditions which must interfere with the normal cycle of carbohydrate break-down. In the untreated, severe diabetic, there must be a deficiency of insulin in the blood and tissues; insulin acts in the carbohydrate cycle by inhibiting the inhibitory activity of the diabetogenic hormone on hexokinase, and also in the tissues by producing or preserving oxalo-acetate, one of the compounds in the cycle essential for the complete destruction of acetic acid. If there/

there is a deficiency of insulin, the tricarboxylic acid cycle will be interrupted and various abnormal compounds will collect in the tissues. It is possible that these compounds may cause the clinical features of diabetic cramp in the same way as Lewis's "P" Factor can cause ischaemic muscle pain. If, however, this were the case, diabetic cramp would tend to occur particularly when carbohydrate or fat break-down was occurring, i.e. during periods of exercise and not at night. In some untreated diabetics pain does occur in their muscles when they take exercise; also it must be remembered that pain is always associated with muscle spasm in diabetic cramp and when the spasm is relieved the pain disappears.

Although the development of the ulcers on the feet may have been influenced by other factors, the principal factor in their aetiology was the neuritis. The history of sores which refuse to heal is characteristic of trophic and neuritic lesions. Loss of sensation in the feet leads to the neglect of small traumata, which enlarge and spread in the surrounding tissue of lowered vitality. The development of neuritic changes four years after the onset of the diabetes is early. The lesions in neuritis are described both in the peripheral nerves and in the central nervous system, and Walshe (1941) attributes them to a breakdown in carbohydrate metabolism at the stage of pyruvic acid due to a deficiency of Co-carboxylase or aneurine. Beattie and Dickson describe diabetic neuritis as a toxi-degenerative process with arteriosclerotic changes in the small blood-vessels which may be responsible for the changes in the nerves, and degenerations in the dorsal columns of the cord. Lawrence⁽¹⁹⁴⁵⁾ is of the opinion that vascular degeneration is rare within ten years of the onset of diabetes in young patients and does not entirely agree with the theory that/

that hypercholesterolaemia may be the cause although he recommends that steps should be taken to deal with it if the blood cholesterol exceeds 200 mgm.% - as it does in this patient. In this patient the changes can be attributed to degeneration in the dorsal columns and lateral columns and the weakness and tiredness of his legs might be due to peripheral neuritis. Thus several of this patient's present symptoms may be due to disturbed carbohydrate metabolism, and so the administration of aneurine is well justified.

Progress and Treatment.

While he was in hospital, treatment to his ulcer was very successful. Rest and protection from trauma, together with chemo-therapy, prevented further irritation and strain on the affected area and caused the disappearance of the infecting organisms. Thus the tissue devitalized to some extent by the loss of its nerve-supply was allowed to recover. The recovery was rapid but was not so rapid as could be expected in normal tissue. Strict control of the diabetes would increase the rate of recovery and the administration of aneurine would assist the progress of the neuritis. However, the latter must be continuous and concentrated for its effects to be of value and it was unfortunate that it was stopped when the patient was discharged. The period of rest produced great alleviation of the cardiac insufficiency and asthma and bronchitis, so that administration of digoxin when the patient was discharged was unnecessary.

In view of the fact that the blood cholesterol was found to be raised, it would be advisable to reduce the patient's fat intake and give him more carbohydrate and perhaps insulin, even though there are few indications of arteriosclerosis at present and although the ultimate effect of raised blood cholesterol is uncertain./

uncertain. In a patient with neuritis and some degree of cor pulmonale, the addition of advanced hypertensive disease would be disastrous.

The question of whether surgery may be necessary to deal with the ulcerated foot must be considered. The break-down of the ulcer after discharge from the R.I.E. shows either that the patient has taken insufficient care of his feet or that there is so much devitalization that further ulceration cannot be prevented. Probably both factors have played a part. The patient should be advised now to take care of his feet and warned that he must do so. If no retrogression then occurs, and if the ulceration shows signs of spreading or enters the underlying bone and it becomes infected, surgical removal will be necessary. If the condition is neglected in its present state, infection and further spread will sooner or later occur and the final treatment will be much more difficult.

Conclusion.

Several pathological conditions are present in this patient. It is probable that the varicose veins, the asthma and the hypertension have a familial origin and that their onset and progress were accelerated by the patient's active life. The endocrine disturbance is of long duration and has influenced the patient's metabolism in other ways than the breakdown of carbohydrate metabolism. It may be responsible in some unknown way for hastening the onset of vascular disease, but if this is so it has caused sufficient damage only in the vessels of the nervous system as yet to produce signs and symptoms: the renal and retinal vessels are still unaffected. It would be of great value if it were known why such a distribution of vascular lesions tends to occur. This cannot be determined from a consideration of this case, but if degeneration in the nervous system/

system is caused by lesions in the small arteries, available evidence suggests that the latter may be preceded by disturbed carbohydrate metabolism in the nervous and possibly muscle tissues.

A suggestion for the origin of diabetic cramp has been made. Experimental evidence of whether a deficiency of insulin in the tissues showing this disturbance, could be obtained by making local intra-arterial injections of insulin into the affected limb and observing its effect on the pain and muscle spasm. Rapid changes of the blood-sugar level may be responsible for precipitating diabetic cramp in controlled diabetes, by producing in the tissues temporary high sugar concentrations which cannot be metabolised properly. Thus it might be possible to produce diabetic cramp for experimental purposes in a diabetic by producing sudden blood sugar level changes. If such experiments were carried out, careful control would be necessary since the observations would depend on subjective impressions of the patient; thus it would be advisable to try to evolve a method of objective measurement of the associated muscle spasm.

In this patient multiple pathology is present. Pituitary dysfunction cannot be treated effectively at present by hormonal substitution. In spite of this, the pancreatic hormone can be used for effective treatment even when it is believed that the pituitary is at fault. Permanent pathological change has occurred already, due to the dysfunction of the pituitary, and even if the exact nature of the pituitary lesion were known, substitution hormonal therapy would be ineffective in curing this pathology. For treatment to be effective in preventing the onset of the diabetes and nervous lesions, a knowledge of the factors which are instrumental in producing the initial glandular degeneration is essential and substitution therapy with hormones after/

CASE 17

after these lesions have occurred can only be palliative and, in the present state of knowledge, may be ineffective, since the exact nature and action of all the endocrine secretions are unknown.

CASE IV

Dr. R. W. D. TURNER.

Mrs. PETERINA BENNET

Ward C.17,

Western General Hospital,

Edinburgh.

DIAGNOSIS: DIABETES MELLITUS WITH
 RENAL AND CARDIO. VASCULAR
 COMPLICATIONS.

MRS. PETERINA BENNET

aet 63 years.

3, East Cromwell Street,
Leith.

married.

Occupation: Housewife

Doctor: Dr. Gilruth,
1, Derby Street,
Leith.

Date of admission: 18.12.48

Date of Examination: 22.12.48

Date of Discharge: 21.1.49.

Complaint: Tiredness and increasing breathlessness for four weeks; dryness of the mouth for four weeks, swelling of the legs for four days.

HISTORY

History of Present Illness

The patient was quite well until the beginning of July 1948. An attack of breathlessness occurred one night which, woke the patient up, which caused very considerable distress, and which forced her to sit up in bed and struggle for breath. She was unable to get to sleep and if she lay down flat in bed the breathlessness became worse. She had no pain. The attack wore off after about half an hour and the patient was able to lie down and go to sleep. She stayed in bed for three days after this attack. She got up and resumed her work after this rest; her work is normally fairly hard and consists of the washing and housework for her family and the all the shopping, which she does at a near-by store to which she can walk in about three minutes. She lives in a flat at the top of three flights of stairs up which she normally could walk easily and without the necessity of resting. When she resumed her housework she found that coming back from the store made her breathless and that literally she had to drag herself

herself up-stairs by the bannisters and needed several rests on the way. She also became breathless on doing strenuous housework and while washing the clothes. A few days later she noticed that after going out shopping or after standing about for a short period her feet began to swell. The swelling first appeared in the left leg and gradually involved the whole foot and then the calf of the leg. It appeared slightly later in the right leg and was never so marked on this side; the swelling was worse at the end of the day and her shoes marked her feet. The swelling gradually became more severe and the patient began to feel tired; her legs felt tired and heavy although at no time did she suffer from any actual pain or cramp in the lower limbs. Finally she called in her doctor towards the end of July and he sent her into Leith Hospital.

She was treated there by rest and medicine for the breathlessness and swelling and as a result of examination of her urine the patient was found to have diabetes mellitus, for which she was treated by dietetic means, but was given no insulin. She was discharged from Leith Hospital after six weeks with no swelling in her legs and with a considerable reduction in her breathlessness. On discharge she was given a diet sheet which she was told firmly to abide by and also told to take no sugar, salt or sweet foods. She was also told to take some medicine in the form of *digitalis* tablets.

The diet consisted of:-

7.00 a.m.	Tea and Toast.
4.00 a.m.	Tea and toast or a slice of bread Porridge.
11.00 a.m.	A cup of bovril.
1.00 p.m.	Meat or fish. Vegetables and potato Pudding.

4.00 p.m. Tea and Toast or a slice of bread.

Egg.

7.00 p.m. Tea or milk

Cheese and vegetables

Brown Bread.

She was encouraged to eat as much meat and fish as possible and large quantities of vegetables amongst which she stressed ^{told} that she had been/to eat lettuces.

On discharge she abided by this diet to the best of her ability but she did her cooking with salt, "occasionally" put some sugar in her tea, and had a cake every now and again. When she returned home she found that her legs felt very tired all the time and uncomfortable and heavy when she had to stand about or walk out to do her shopping. They were especially uncomfortable when she came home from her shopping and started going up stairs to her flat. However she did not notice them swelling at any time. She found she was unable to do all her housework properly or easily and that she rapidly became exhausted. She suffered from breathlessness when going upstairs and had to pull herself up and have several rests on the way.

She remained in this condition till about four weeks before admission to the Western General Hospital when she began to notice that her mouth felt "as dry as a stick". She began to cough about this time but brought up little sputum, and developed a cold. As a result of this she stayed in bed for much of the time for the next three weeks although during the day she got up periodically to do some housework and as she said "to run about". Four days before admission her feet and legs began to swell, first the right foot and leg and then the left although it was at no time so bad as the right. She immediately called her doctor who sent her into hospital. She has always been constipated and takes

takes syrup of figs every other day as a result of which she has a regular bowel movement. For many years she has had to get up three times each night to pass urine which she thinks has been of a normal light yellow colour. She says she has had no vulvar itching at any time. She has not been any hungrier prior to admission and does not consider that her output of urine has increased. About seven or eight years ago she states that she was a large fat woman but about this time began to lose weight and after two or three years was about the weight which she now is and looked thin and small like she now appears. The menopause occurred when she was aged forty and since then she has had no discharge and passed no blood.

Previous History

When she was about twenty years old her left foot was poisoned. She was put to bed and the foot was incised. She had to stay in bed for six weeks after which the foot had completely healed. Ever since then the left leg has always been larger than the right and has tended to swell after the patient has been standing for a short time although swelling never occurred in the right leg.

Five years ago at Christmas time after returning home from a walk and while she was sitting in her chair the patient suddenly felt giddy and faint, suffered from an aching pain in the left side of her chest and almost collapsed. She suffered from discomfort and palpitations in her chest. She went to bed and stayed in bed next day and on the day following she noticed that she had no power in her right arm, shoulder and right side of her face. Her mouth was drooping on the right side and her speech became like that of an infant. Her doctor was called in and reassured her, told her the condition would clear up and that she would have to stay in bed. The condition gradually improved

improved and after six weeks was completely better, all the muscle power having returned to her limb and her speech having recovered completely although her mouth remained twisted. Apart from these two illnesses the patient says she had no illnesses in her child-hood. She attributes and traces back the cause of her present condition to her illness five years ago. She says she has never suffered from sore throats and never had scarlet fever. There is no history of previous attacks of oedema or symptoms suggestive of nephritis.

Family History

The patient's father and mother both died at an advanced age. They both had been very healthy all their lives. Two brothers, one of whom is aged 72, are both well. A twin sister is also alive and well. The patient's husband is a night watchman and is well. The patient has two sons who have both always been healthy. A third son died at the age of three as a result of measles. There is no family history of cardiac or renal disease or of diabetes.

Social History

The patient lives with her husband and one son in a flat up three flights of stairs. It contains a kitchen and two rooms. The flat is comfortable and the family is happy and contented. The patient does not smoke or take alcohol.

PHYSICAL EXAMINATION

General Inspection

A thin pale old lady. There is no colour in her cheeks and her malar bones ^{are} prominent. Her hair is gray and thick. Her mouth droops towards the right side. Her eyes are watery and the conjunctivae are slightly congested. Her neck is thin and her sterno-mastoid muscles are small. There are no changes in her hands or fingers. She is not cyanosed and is continually licking her lips.

lips.

Temperature : 97° F

Cardio-Vascular System

Pulse:

Radial Pulse: The vessel wall is palpable and thickened. The calibre of the vessel is large. The rhythm is normal, the pulse wave well sustained, the volume regular but large and there is no diastolic.

Rate : 100/minute.

Blood Pressure : 190/110.

Pulses in the lower limbs:

Dorsalis Pedis: Both pulses palpable, that in the right foot being stronger, although it is only about half as powerful as the radial pulse.

Posterior Tibial: The left is impalpable: the right is palpable but weak.

Popliteal : Neither pulse could be felt.

Femoral : Both palpable and strong.

Ophthalmoscopic Examination:

Cataract in left cornea.

Right Eye:

The margin of the disc is definable and is partly outlined by pigment. The retina is pale red in colour but has numerous white exudates of varying sizes scattered over it. In places there are small dark red haemorrhages which often lie in relation to the exudates, there are also small haemorrhages near the arteries. The arteries are tortuous and near the disc show slight silver wiring. The veins are full but do not appear to be compressed where the arteries cross them. The macular region is normal.

Precordium :

There is no venous congestion in the neck or over the chest wall. There is no visible pulsation in the neck, chest

chest or abdomen, the apex beat is not visible.

The apex beat is impalpable while the patient is lying down, but when she sits up and leans forward it is palpable in the fourth inter space five inches from the mid-line.

There are no palpable thrills or friction.

The area of cardiac dullness was determined by percussion:

the left border is

1½ inches from the mid-line in the 2nd inter-space.

3 " " " " " " 3rd " "

5 " " " " " " 4th " "

the right border is one inch from the mid-line.

In the mitral area the heart sounds are of equal intensity due to an abnormally loud first sound. The heart sounds have a normal rhythm but they have a tic-tac quality. There is a soft blowing systolic murmur co-existent with and following the first sound. It is not propagated into the axilla but extends up the left side of the sternum and has its maximum intensity in the 3rd inter-space, though it can also be heard in the 2nd inter-space.

In the aortic area the 2nd sound is accentuated. There are no murmurs.

In the pulmonary area the sounds are normal but there is a faint systolic murmur propagated from the mitral area.

In the tricuspid area the heart sounds are normal.

Respiratory System

The patient breathes normally through her nose.

Respiration Rate : 17/minute.

Chest :

A long chest with narrow subcostal angle. Regular shallow thoracic respiration.

Chest expansion : ½ inch, equal on both sides in the upper lobes but diminished in the lower left lobe. No palpable friction or rales. Vocal fremitus normal in both

both lungs anteriorly but posteriorly it disappears at the 9th rib on the left side and at the 10th rib on the right side.

On percussion the note is stony dull posteriorly at the level of the 9th rib on the left side and at the 10th rib on the right. The dullness extends up to the 7th ribs in the mid axillary lines. Anteriorly the breath sounds are vesicular. Posteriorly they are broncho-vesicular over the lower lobes. Medium crepitations can be heard at the end of inspiration over the upper and middle areas of the lower lobes. Vocal resonance is diminished over the lower areas of the lower lobes.

Alimentary System

Mouth :

The lips : pale red, dry.

Tongue : white coating except along the margins.

Dry.

Tonsils and oral Pharynx : Normal.

Teeth : all false. Well-fitting.

Abdomen :

Abdominal wall : lax and soft. No distension rigidity or tenderness.

Stomach and Intestine : impalpable.

Spleen : impalpable.

Liver : on percussion dullness detected $\frac{1}{2}$ an inch below right rib margin. Some resistance is palpable below the rib margin. Slight liver tenderness. Hepato- jugular reflux present.

Urinary System

Right Kidney :

Hard, mobile, palpable about one inch below the rib margin.

Left Kidney :

Impalpable.

Urinary findings given under Progress.

Progress.

Endocrine System

Thyroid gland : No abnormality detected.

Lymphatic system : no glands palpated in axilla or neck. Small superficial glands felt in the groins.

Breasts : Some thickening and nodulation detected in each breast supero-lateral to the nipples.

Nervous System

Mental state :

The patient is an old lady who has difficulty in understanding and answering questions and who tends to wander off the subject when answering. Her answers vary when the same question is put to her more than once and she gives a rambling history. She is very ^sconscious of her illness and uses it as an excuse for getting attention and for trying to prevent anyone from examining her. She is very anxious to get out of hospital and thinks she is benefitting very little from hospital treatment.

Cranial Nerves :

The patient uses glasses for near vision. Her pupils are equal but the left is slightly irregular.

The patient's mouth is slightly asymmetrical and droops on the right side to a small extent. No weakness can however be detected in the orbital or oral muscles of the right side of her face. No abnormalities detected in cranial nerve function.

Spinal Motor Nerves :

Muscle power is equal and moderately strong in the upper and lower limbs. Muscle tone is normal and there is no muscle wasting or tremor in the limbs.

Spinal Sensory Nerves :

No abnormalities detected in pain or light touch sense in any area. Muscle and tendon pressure sense normal.

normal. Joint sense normal.

Vibration sense :

	Left lower limb	Right lower limb
Metatarsal-Phalangeal Joint	—	+
Tibia	—	+
Patella	—	+
Reflexes :		

	Upper limb	
	Right	Left
Biceps	+	+
Brachio-radialis	—	—
Triceps	—	—
	Lower limb	
Knee	+	+
Ankle	+	—

The lower limb reflexes could only be obtained with reinforcement.

Plantar responses : both flexor.

Skin and Subcutaneous Tissues

The eyelids are puffy and moist, and the conjunctivae are congested.

Pitting oedema is present on the dorsum of the hands and there is slight oedema in the region of the elbow and triceps insertion in each limb. The fingers are normal and the hands and arms are thin. There is extensive sacral oedema which extends up to the level of the iliac crests.

Right lower limb : deep pitting oedema in the foot, round the achilles tendon, in the calf, round the knee and extending onto the posterior surface of the thigh for $5\frac{1}{2}$ inches above the adductor tubercle.

Left lower limb : deep pitting oedema as in the right limb which extends onto the posterior surface of the thigh for 4 inches above the adductor tubercle.

tubercle.

Locomotor System

Nothing abnormal detected.

Examination of the Blood

Red blood cell count : 4,800,000 per cubic m.m.

White blood cell count : 7,100 per cubic m.m.

Special Examinations

All the Esbach tests were carried out on the morning specimen of urine.

18.12.48 Specific gravity of urine : 1010

20.12.48 Electrocardiographic Examination:

Blood Pressure : 210/110

Pulse Rate : 101/minute

Normal Sinus Rhythm

P R Interval : 0.14 second

Q R S Interval : 0.06 second

P Wave : Low upright

Q R S Complex : Low voltage R III

R S T Interval : Normal depression R S T II

T Wave : Low upright T I ; Flat T II and T III

Normal Axis

Compatible with Left Ventricular Hypertrophy.

Examination of Stool.

Benzidene : Negative

Examination of Urine.

24 hour collection :

Volume : 35 oz.

Specific gravity : 1028.

Esbach : $3\frac{1}{2}$ gm/litre.

Microscopic Examination : more than 10 white blood cells seen per high power field.

21.12.48 Bacteriological report on catheter specimen of urine.

urine.

Film : a few pus and epithelial cells and some coliform bacilli.

Culture : a scanty growth of B. aerogenes.

Plasma Proteins :

Total 5.7 gm. %

Albumen 3.3 gm. %

Globulin 2.4 gm. %

Radiological Report on Chest.

The heart is enlarged. There is a pleural effusion at each costophrenic angle especially on the right side. Heart failure is present.

22.12.48 Glucose Tolerance Test :

50 gms. glucose given orally after the first specimen of blood had been taken.

Zero Time 248 mgm. %

$\frac{1}{2}$ hour 262 mgm. %

1 " 319 mgm. %

$1\frac{1}{2}$ " 356 mgm. %

2 " 371 mgm. %

22-23.12.48 Examination of Urine.

24 hour collection :

Volume : 20 oz.

Specific Gravity : 1024

Esbach : $3\frac{1}{2}$ gm/litre.

25.12.48 Examination of Urine.

Reaction : acid

Specific Gravity : 1020

Ketones : absent

Esbach : 3 gm/litre.

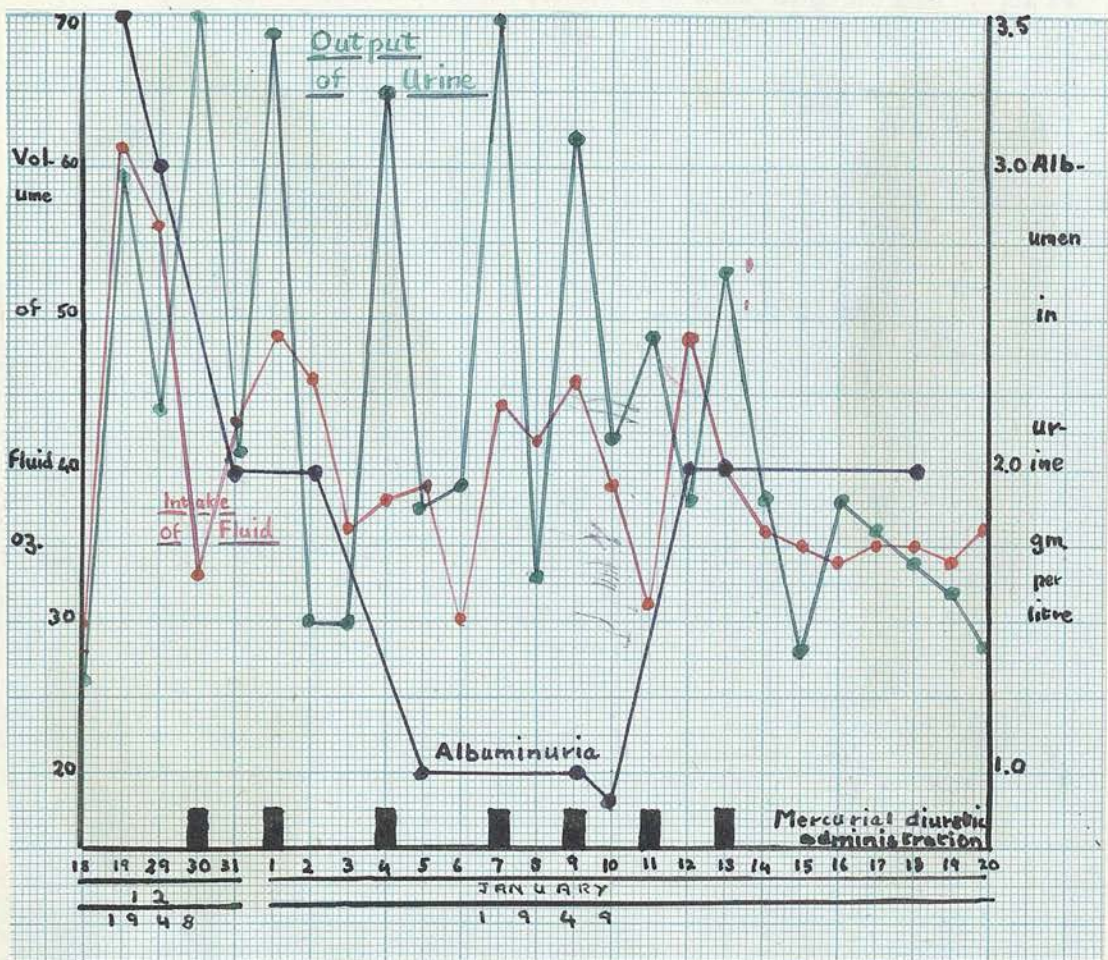
26.12.48

Esbach : 2.6 gm/litre

27.12.48

Examination of the blood

Haemoglobin : 95 %



Graph to show the effect of administration of mercurial diuretics on the intake of fluid and the output of urine. Until 29.12.48 the albuminuria varied between 3 and 4 gm./litre daily; following this it decreased as shown in the graph.

Haemoglobin : 95 %

Red blood cells : 4.1 million/cu.m.m.

White blood cells: 8,400 / cu. m.m.

Esbach : 4 gm/litre

28.12.48 Blood Urea Nitrogen : 17 mgm. %

29.12.48 Esbach : 3 gm/litre

30.12.48 Microscopic Examination of the Urine:

Numerous pus cells and a few red blood cells present. No casts.

31.12.48 Esbach 2 gm/litre

2.1.49 Esbach 2 gm/litre

4.1.49 Bacteriological Report on Catheter specimen of urine.

No abnormalities seen in Film.

No growth.

5.1.49 Microscopic examination of urine:

Numerous pus cells present.

No Red blood cells.

No casts.

Esbach : 1 gm/litre

6.1.49 Bacteriological Report on catheter specimen of urine

Many epithelial cells and coliform bacilli seen in Film.

No pus.

Moderate growth of B. coli.

9.1.49 Esbach : 1 gm/litre

9-10.1.49 Examination of Urine.

24 hour collection

Volume : 62 oz

Reaction : acid

Specific Gravity : 1008

Esbach : 0.9 gm/litre

12.1.49 Esbach : 2 gm/litre

13.1.49 Esbach : 2gm/litre
18.1.49 Esbach : 2gm/litre
20.1.49 Blood Urea Nitrogen : 17 mgm %
CO₂ Combining Power : 55 vol. %
Blood Cholesterol : 247 mgm %

Urea Clearance Test :

Specimen I

Urine Urea Nitrogen : 632 mgm %

Volume : 19 c.c.

Clearance : 39 % of normal

Specimen II

Urine Urea Nitrogen : 593 mgm %

Volume : 27 c.c.

Clearance : 44 % of normal.

18.12.48 Estimation of the

- 21.1.49 Urine sugar.

From 18.12.48 until 23.12.48

A red colouration was produced when the urine was tested with Fehling's solution in every specimen.

From 24.12.48 until discharge only a trace of sugar was detected once or twice daily. The urine sugar was estimated in four specimens each day.

TREATMENT

The treatment was directed towards the control and improvement of the clinical features produced by

- (1) The renal damage
- (2) The pathological condition of the heart and vascular system.
- (3) The diabetes mellitus.

18.12.48 The salt and fluid intake were restricted. No salt was allowed at meals and the cooking was carried out with a minimum of salt.

Digoxin : 0.50 mgm.

Digoxin : 0.50 mgm.

Chloral : 20 gr.

19.12.48 The diet was arranged to consist of :

Carbohydrate 148 gm

Protein 87 gm

Fat 114 gm

Digoxin : 0.25 mgm. Q.I.D.

20.12.48 Digoxin administration was stopped and it was decided to treat the patient for Diabetes Mellitus alone.

22.12.48 Soluble Insulin : 10 units in the evening.

23.12.48-26.12.48 Soluble Insulin : 10 units B.I.D.

27.12.48 Soluble Insulin : 10 units T.I.D.

28.12.48 - Protamine Zinc Insulin : 10 units and Soluble

-7.1.49 Insulin : 10 units daily.

30.12.48 It was decided to attempt to lessen the oedema by the use of mercurial and other diuretics.

Neptal : 2 c.c. 1.V.1.

1.1.49 Metsalyt : 2 c.c. 1.V.1

3.1.49 Ammonium Chloride : 30 gr.

4.1.49 Ammonium Chloride : 30 gr.

Salyrgan : 2 c.c. 1.V.1.

7.1.49 Neptal : 2 c.c. 1.V.1.

8.1.49 - 14.1.49 Protamine Zinc Insulin :
10 units, and Soluble Insulin:
10 units daily.

8.1.49 Syrup of Codein Phosphate:
2 fl. dr.

9.1.49 Neptal : 2 c.c. 1.V.1.

11.1.49 Neptal : 2 c.c., and Novocain:
1 c.c. 1.M.1.

13.1.49 Neptal : 2 c.c. 1.V.1.

15.1.49 - 17.1.49 Protamine Zinc Insulin:
10 units : and Soluble
Insulin: 5 units daily.

18.1.49 - 19.1.49 Protamine Zinc Insulin:
5 units : and Soluble
Insulin : 5 units daily.

20.1.49 - 21.1.49 Protamine Zinc Insulin :
5 units daily.

21.1.49 Discharged. The patient was instructed to
take a 2000 calorie diet but was not told to take
any insulin.

PROGRESS

The patient's progress was measured by changes observed in
(1) The renal and cardio-vascular condition as shown by the
state of the oedema, changes in weight, and examination of the
urine and blood. The latter examinations have already been
given under Special Examinations.

(2) The diabetic condition as shown by blood sugar, and urine
sugar estimations.

29.12.48 On percussion liver dullness extended to just below
the rib margin, but the liver was neither palpable nor tender.
The hepato-jugular reflux could not be obtained.

Blood pressure : 170/105

There was no change in the degree of oedema in the chest,
trunk or limbs. The patient feels tired and is rather
querulous. She is of opinion that no improvement is taking
place and wishes to be discharged.

3.1.49 The oedema is lessening. It is still present in the
chest and the physical signs are unchanged. Over the
sacrum it is diminishing and it can be detected only up
to a point 2 inches above the adductor tubercle on the
left leg and one inch above it on the right leg.

leg. Blood Pressure : 180/110

The patient is more cheerful and is willing to continue treatment.

5.1.49 Oedema is diminishing in the chest. In the axillae it is receding and dullness is not so marked over the lower lobes posteriorly.

There is still some sacral oedema but oedema only extends up to a point 5 inches below the left adductor tubercle and 7 inches below the right adductor tubercle.

It is absent over the dorsum of the right foot.

Blood pressure : 165/110.

7.1.49 Examination of the Fundus Oculi by Ophthalmic Surgeon:

The Fundal changes are of hypertensive origin: there are no diabetic changes.

11.1.49 Oedema is present round the right achilles tendon and in the left foot. Sacral oedema is only slight but there are still signs of oedema in the chest.

15.1.49 Oedema has disappeared from the sacrum and right leg. It is still present in the left foot and dullness is present over both lung bases and there are a few basal crepitations.

The patient objects to her injections of mercurial diuretics and insulin and says she will not give them to herself so her son is being taught how to inject insulin.

16.1.49 The patient will be allowed up for short periods each day.

21.1.49 Discharged.

Oedema is present in the right foot and there is some dullness over both lung bases.

Blood Pressure : 160/90.

DISCUSSION.

Diagnosis.

The diagnosis of diabetes mellitus can be made in view of the history of dryness of the mouth, polyuria and tiredness, as a result of the discovery of sugar in the urine, and from the effect of insulin and dietetic therapy. The difficulty in diagnosis in this case was in deciding to what extent the cardio-vascular and renal systems are responsible for the clinical features, and whether cardio-vascular or renal pathology is dependent initially on the disturbed carbohydrate metabolism. Diabetes mellitus may precipitate the onset of cardio-vascular disease and more rarely the onset of pathological changes in the kidneys; alternatively cardio-vascular disease by reducing the blood-supply to organs controlling carbohydrate metabolism may be responsible for the occurrence of diabetes. Disease of the endocrine system as shown by changes in other glands besides the pancreas may also cause hyperglycaemia. Before a diagnosis indicating the precise pathology can be made, the features which can be attributed to disorder in each of these systems must be discussed. Until it is decided definitely which system is principally at fault, no prognosis can be given or rational therapy applied.

Pathology and Course of the Disease.

The patient stated that she was a healthy and active woman until her illness five years ago. The history of this illness is characteristic of a myocardial infarct and the subsequent paralysis could be attributed to a cerebral embolus which had its origin in the heart, and was released from a thrombus which had formed over the infarcted area of myocardium. Coronary occlusion commonly occurs in patients who have had a previous history of anginal disease but this need not always be present./

The patients generally present signs of arterial disease, and usually a high blood pressure. This patient had a hypertension while she was in hospital and it is improbable that such a degree of hypertension could have arisen since the illness five years ago. The occurrence of the attack while the patient was sitting down, the continuous, left-sided, aching pain, the collapse and the palpitations in the chest produced by disordered cardiac rhythm are characteristic of this condition. Endocardial as well as myocardial involvement commonly occurs and it is usual for blood clot to form on the affected area of endocardium. It is not usual for emboli to be released from the thrombus within two days of the occurrence of the coronary infarct; however, this might occur if a large area of endocardium was involved and a large clot had formed. It is possible that a clot may already have been present in the heart, produced by an earlier small unrecognised coronary occlusion, or in the aorta which is probably atheromatous, and that as a result of the disordered heart action following the present infarction an embolus was released from it and lodged in the brain.

The patient states that breathlessness and oedema did not appear until the middle of 1948. The patient is not a good witness and it is probable that signs of cardiac failure had been present for some time before the attack of nocturnal dyspnoea in July 1948. The nocturnal dyspnoea and breathlessness are features of left ventricular failure; the attack of nocturnal dyspnoea was severe and, although some right-sided failure was probably present at this time, this attack of left-sided failure must have increased the right-sided failure to such an extent that it began to intrude on the patient's notice in the form of the clinical features of/
of/

of venous congestion.

Clinical investigation shows that vascular disease is present both in the peripheral and retinal vessels. This vascular disease probably influenced the onset of left ventricular failure, the precipitating factors being -

- (1) Essential Hypertension. This has probably been present for some time, as is indicated by the advanced state of degeneration of the limb vessels and retinal vessels.
- (2) Coronary Artery Disease. This is a feature of the generalized vascular disease but in that it caused cardiac damage it probably hastened the onset of left ventricular failure. The systolic pressure is still high and thus either it must have been very high before the myocardial infarct, or the infarct must have involved only a small part of the heart muscle with little resultant effect on the systolic pressure. The latter is more probable since there is no history of symptoms of high blood pressure and the symptoms of cardiac disease had disappeared completely in six weeks.

The occurrence of oedema is a more recent development. The factors which may have been responsible for it must be discussed.

(1) Congestive cardiac failure is the chief factor responsible for the oedema. Its initial appearance in the lower limbs, its increasing severity as the day wore on, its first appearance in the leg which had already suffered from a disease which must have interfered with venous drainage, and its gradual progress up the legs as the patient's condition deteriorated are all signs of a gravitational oedema due to disease of the heart. This is further confirmed by the discovery of oedema over the sacrum and in the lung bases when the/

the patient was in bed, positions where the oedema characteristically collects in congestive failure. That congestive cardiac failure was present is shown on clinical examination by the presence of the hepato-jugular reflux and enlarged and tender liver. However, in the presence of such signs it is difficult to understand why the jugular venous pressure was not raised since according to Lewis (1948) these signs generally occur together.

(2) In spite of the large loss of protein in the urine, the blood protein level was not outwith the normal limits. The plasma albumen was at the lower limit of normal and the plasma globulin was at the middle of the normal range. The total plasma protein was 5.7 gm.% and it is stated that hypoproteinaemic oedema does not usually occur until the plasma proteins are below 5.0 gm.% or the albumen below 2.5 gm.% (Stewart and Dunlop, 1949, p. 179). It is possible that these levels may have been reached before the patient was admitted and that some of the oedema was due to hypoproteinaemia but the only clinical feature to support this was the slight puffiness of the eyes, which may have been due to conjunctivitis. There was no generalized oedema or history of it, which is characteristic of a hypoproteinaemic origin.

(3) The patient's diet before admission to hospital contained a large proportion of food which is rich in Vitamin B, such as porridge, bread and meat. It is probable that her diet contained even more of these foods before she was treated for the diabetes, and so it is unlikely that her oedema and congestion were due to beri-beri. The only features suggestive of this condition were the rapid pulse and cardiac enlargement which can be explained as a result of the high systolic pressure in the presence of hypertension. In such circumstances/

circumstances cardiac hypertrophy is to be expected as well as some dilatation. It is difficult to explain why the former was not found on electro-cardiographic examination in spite of the fact that on clinical examination the heart was found to be enlarged.

The absence of any signs of neuritis, together with the absence of any indication of dietetic deficiencies, make it unlikely that beri-beri was present.

The diagnosis of Diabetes Mellitus can be made with certainty but it is not easy to determine how long this condition has been present. The patient passed through her menopause without any severe symptoms. Until eight years ago she was a fat woman; at this time she suddenly began to lose weight. Mild diabetes commonly occurs in elderly fat patients and this may have occurred in the patient eight or more years ago. Since she had no treatment, the condition may have progressed and, as a result of this, she lost weight.

The onset of the diabetes was relatively symptomless. In spite of this the glucose tolerance test showed a high climbing curve characteristic of severe diabetes. Such a finding is unexpected in this patient because in elderly diabetics with a short history a more normal curve is often obtained. The reason why such a response was obtained is probably that control of the diabetic condition had been very ineffective prior to admission, with a resultant decrease in the carbohydrate tolerance. This is borne out by the fact that on discharge only dietetic treatment was required in order to maintain control because energetic insulin therapy had restored the carbohydrate metabolism to normal and enabled the pancreas to resume a large part of its physiological activity.

The passage of urine three times a night is not normal
in/

in a woman of this age and is probably due to the hyperglycaemia. These features make it probable that the patient has been suffering from diabetes for at least eight years and possibly longer. Thus the diabetes was present at the time of the myocardial infarct.

Arteriosclerosis is a frequent accompaniment of diabetes and is demonstrable in the larger vessels both clinically and post-mortem by the discovery of atheromatous changes in the aorta, coronary and cerebral vessels, and in the smaller vessels, by the presence of hypertension and retinal changes and by microscopic post-mortem examination. (Diabetic complications in the nervous system or cardio-vascular system occur most commonly in cases where the onset of the disease has been very severe or it has been untreated for a long period. These complications seem ultimately to be traceable to vascular disease, whether they show themselves by nervous or renal clinical features.) The relation between arteriosclerosis and diabetes is unknown, but it is generally believed that there is some relation between them and that in diabetes vascular disease is particularly prone to occur. In this patient, both types of arterial degeneration were present, as is shown by the occurrence of the myocardial infarct as a result of coronary disease, and by the presence of hypertension and changes in the retinal vessels. In the latter there are signs of arteriosclerotic change as it is defined by Croom and Scott (Lancet, 1949). Retinopathy was also present. The ophthalmologist stated that it was of arteriosclerotic origin. According to Croom and Scott, some factor other than arteriosclerotic change is concerned in the production of retinopathy in the diabetic patient; but, unless it is known before the examination that the patient is diabetic, and not arteriosclerotic, there seems to be no way of/

of differentiating arteriosclerotic and diabetic retinopathy, since the conditions which Croom and Scott state are necessary to diagnose retinopathy in a diabetic might equally well be present in an arteriosclerotic patient without diabetes. Thus, unless there are changes in the fundus which Croom and Scott do not describe, by which diabetes may be diagnosed, it seems that it is not possible to determine whether the retinopathy is due to arteriosclerosis or diabetes in a patient such as this, who suffers from both conditions. This patient's hypertension has arisen as a result of vascular disease: such disease might have occurred had the patient not suffered from diabetes; and even though the diabetes has been present for some years, it is quite probable that the vascular disease has been present for longer. The occurrence of diabetes probably accelerated the vascular disease and this acceleration may have been encouraged by the lack of treatment of the diabetes. Evidence at present indicates that diabetes and vascular disease are in some way related but there seems to be insufficient evidence to attribute the vascular changes in a diabetic patient to the diabetes alone.

The oedema may be attributed to primary renal pathology, or to pathological changes in the kidneys secondary to changes elsewhere in the body.

That some impaired renal function is present is shewn by the albuminuria and diminished urea clearance. This impaired function might have been caused by.-

(1) Congestive failure. Albuminuria is commonly present in congestive failure. If it is due entirely to the congestive failure the albuminuria will disappear as the failure improves, and if there is no associated nephritis the patient should be capable of passing urine with a specific gravity of over/

over 1020 (Stewart and Dunlop, 1949, p. 99). As this patient improved, the albuminuria became less and on discharge it was 2 gm./litre less than it had been on admission. While she was in hospital several specimens of urine with a specific gravity of over 1020 were passed. Thus it may be concluded that at least some of the albuminuria was due to the cardiac failure. However, the fact that albuminuria was still present when the signs of cardiac failure had disappeared suggests that there was some renal pathology also.

(2) Benign Renal Arteriosclerosis. In this condition the clinical findings vary according to the degree of renal damage. There are however in this condition fairly large areas of normal kidney tissue and, as a result, renal function tests do not usually show gross change. Some albuminuria occurs but it would not be as massive as in this case. Nocturnal polyuria is often a symptom of this condition but by itself is not diagnostic of it. There probably is some renal damage caused by the vascular disease but it is unlikely that it could alone account for the clinical features.

(3) Kimmelstiel-Wilson Syndrome. The features of this case correspond to those described by Gault, Stalker and Lyall (B.M.J., 1948) in elderly patients with a short history of diabetes. This case differs from these workers' patients in that she also had cardiac failure. These workers are of the opinion that the features of their cases could be attributed to associated vascular changes and not to the diabetes itself. They consider that diabetic renal changes may be present but are not the cause of the signs and symptoms.

Such a conclusion is probably supported by the findings in this case. On discharge, this patient still suffered from albuminuria and her urea clearance test was impaired. Some permanent/

permanent renal damage must therefore have been present. This damage probably arose from primary vascular disease, possibly accelerated by the diabetes.

The clinical features can be attributed principally to the vascular disease and the resultant pathological changes in the kidneys and heart. The oedema was principally the result of the cardiac failure. Gauld and his co-workers reported oedema in some cases with plasma protein levels above 5 gm.% though they do not explain why the oedema occurred. In this case the oedema may have arisen partly from hypoproteinaemia caused by the renal damage which resulted from the vascular disease but the main loss of protein was probably due to congestive failure.

Treatment.

In spite of the fact that treatment at Leith Hospital was effective with digitalis and that digitalis therapy was continued until her admission to the Western General Hospital, this therapy was stopped on admission since it was considered that the patient's oedema was of hypoproteinaemic origin. Treatment consisted of rest, diuresis with the aid of mercurial drugs, and treatment for the diabetes. The complete rest in bed, by relieving the burden on the heart, was certain to produce some benefit but it is probable that, had digitalis therapy been effectively carried out, this benefit would have been more rapid. It is unlikely that full digitalisation was achieved before the patient was admitted. If it had been achieved after admission, diuresis might have occurred without the necessity of using the mercurial diuretics. This would have had the advantage that it would have avoided the possibility of further damaging the kidneys with the mercurial drugs.

The control of the diabetes was rapid and effective; and, as control was established, the dose of insulin could be reduced/

reduced. Strict control of the diabetes was necessary since it is probable that the diabetes was responsible, at least to some extent, for the deterioration of the patient's general condition.

When the patient is discharged home it is likely that her condition will again degenerate as a result of the increased work thrown on to the cardio-vascular system. In spite of strict treatment for the diabetes and limitation of her activities, it seems probable that digitalisation will finally become necessary.

In conclusion, it may be stated that a diagnosis of diabetes associated with vascular disease which has resulted in hypertension and signs of myocardial failure can be made. There is some renal impairment also present, but this is principally the result of the vascular disease. There are strong indications for the use of full digitalis therapy as well as strict diabetic treatment, and it is likely that until these methods of treatment are used the patient will continue to suffer from the features, to a greater or less degree, which were present when she was admitted.

Prognosis.

The prognosis depends on -

(1) The progress of the diabetes. If this can be fully controlled, the progress of the vascular disease will be slowed down. The lack of co-operation by the patient makes it unlikely that control will be effective. The occurrence of albuminuria, in the absence of other signs of cardiac failure, is of serious import and must be taken as a warning of early renal complications.

(2) The patient had had one attack of cardiac failure previous to that for which she was admitted to the Western General/

General Hospital, and it is unlikely that she will survive a third attack. The presence of retinitis and oedema are also bad prognostic signs and, according to Gault et al., are an omen of death within the next two years.

If digitalisation, limitation of activity and strict diabetic treatment were carried out, the prognosis would be improved. But even in these circumstances death from uraemia, cardiac failure or embolism would only be delayed, and could not be avoided within a few years.

Conclusion.

A diagnosis was made of diabetes mellitus and of cardiovascular disease. Treatment of the former was applied probably some time after it had arisen and, although this could not cure any pathology to which the diabetes may already have given rise, at least it could control the condition in the future. Treatment of the latter could not hope to provide substitution therapy as is being done with the diabetic condition, but would only lengthen the period before death, due to cardio-vascular disease, occurs.

This case demonstrates how diabetes and cardio-vascular disease can occur together, but the findings suggest that their influence upon one another is small. Permanent renal disease was present; it is possible its progress has been influenced by the diabetes, to a lesser degree, but in the same way as Case V.

CASE V

PROFESSOR D. M. DUNLOP.

MR. JAMES LOWE.

Ward 22,

Royal Infirmary

of Edinburgh.

DIAGNOSIS: DIABETES MELLITUS WITH
RENAL COMPLICATIONS.

Mr James Lowe, aet. 41 years: single.

50 Somerville Street,
Burntisland.

Occupation: Railway Pointsman.

Doctor: Dr Arnott, St Brendan, Burntisland, Fife.

Date of Admission: 27.1.49.

Date of Examination: 31.1.49.

Date of Death: 8.3.49.

Complaint: A heavy cold for three weeks; gradual development of swelling in his legs, body, and face for one week.

HISTORY.

History of Present Illness.

The patient has had diabetes mellitus for twenty years, during which he has been treated by diet and insulin. He has been stabilized with Protamine Zinc Insulin and diet, the dosage of insulin before the onset of his symptoms being 28 units in the morning. He tests his own urine for sugar and varies the dosage of insulin according to his findings. He has kept very healthy under this treatment and has very few reactions.

He had been quite well until a fortnight before admission, when he developed a cold. There was no sore throat but he had a cough and a running nose. He found that he began to lose large quantities of sugar in his urine and this continued even when he increased his insulin dosage to 32 units daily. Three days after the onset of the cold he noticed that his face was becoming slightly puffy round the eyes, and a week before admission some swelling appeared in his legs and ankles. The swelling in his face progressed and was uninfluenced by posture. The swelling in his ankles did not diminish on resting/

resting and was not appreciably influenced by exercise. He sent for his doctor two days before admission, who immediately sent him to the R.I.E.

He has not had any breathlessness, or palpitations in his chest, and there has been no cyanosis. There have been no bowel symptoms. During the last week he has been passing less urine than normal. He has been taking de Witt's kidney pills; while he was taking them his urine was greenish-blue in colour but at all other times it has been of a normal colour and it has never been red or smoky coloured. He does not think that there has been any marked change in his weight recently, although five months ago he weighed 10 stones 2 pounds. He has had no pain or cramp in his legs or any other part of his body since his symptoms started.

History of Previous Illnesses.

The patient developed diabetes twenty years ago, while he was a railway porter. He had no particular worries or colds, or acute illnesses, at this time. He suffered from thirst, polyuria, weakness and tiredness. He had no pain in his legs and no visual disturbances. He consulted his doctor about ten days after the onset of his symptoms and was sent to the R.I.E., where he was stabilized in Ward 21.

Appendicectomy was carried out in 1939, in Ward 7, after which he was admitted to Ward 29 in coma and was again stabilized.

He gets very few hypoglycemic reactions and has always been very healthy. He suffers from one or two colds per year, which last for about a month and have a normal course.

Social and Family History.

The patient is unmarried and lives with his father. He is/

is teetotal and smokes about 30 cigarettes per day.

There is no history of diabetes in the family.

PHYSICAL EXAMINATION.

General Inspection.

Patient is a large, well built man. He is sitting up in bed, reading a book. His face is swollen, particularly round the eyes and in his cheeks. There is severe subconjunctival oedema. He is not distressed in any other way and his hands and arms show no abnormalities.

Temperature: 98.4°F.

Actual weight: 11 st. 13 lbs.

Height: 6 ft. 1 in.

Urinary System.

Kidneys: not palpable: no tenderness detected in the renal areas.

Bladder: not distended.

Urine: Reaction - alkaline
Colour - orange
Specific Gravity - 1034
Albumen - +++
Sugar - +

Microscopic examination - granular and hyaline casts: some epithelial cells.

Cardio-vascular System.

Pulse: regular in time and volume, full strong wave.
The vessel wall is not palpable.
Rate - 84/minute: Blood Pressure 170/70.
The pulses can be felt, and are strong and regular, in the dorsalis pedis and posterior tibial arteries of both limbs.

Precordium: There is no venous congestion or pulsation present in the neck. The apex beat can be seen and felt in the fifth intercostal space in the mid-clavicular line, 3 inches from the mid-line. The beat is localised and of normal force.

The area of cardiac dulness is not increased.

The heart sounds are loud, but are pure and closed in all areas.

Examination/

Examination of the Fundus Oculi.

No abnormalities are detectable. The optic disc is clearly defined and of a normal pink colour. No haemorrhages or exudates are visible in the neighbourhood of the disc or elsewhere in the fundus. There is no irregularity in the walls of the arteries, tortuosity, or constriction of the vessels at the arterio-venous crossings. The macular region is normal.

Respiratory System.

Respiration Rate - 20/minute.

The chest moves equally on both sides: the chest expansion is good.

Vocal fremitus is diminished posteriorly over the lower portions of the lower lobes.

On percussion the note is resonant anteriorly but is impaired in the left axilla and over both bases.

The breath sounds are vesicular and are heard well over the upper lobes, but are difficult to hear posteriorly below the fifth thoracic spine: no crepitations: Vocal resonance is diminished over the base of each lung.

Central Nervous System.

Cranial Nerves: Nothing abnormal detected.

Pupils: equal and regular, react to light and accommodation.

Swallow and palatal reflexes present.

Spinal Motor Nerves: Nothing abnormal detected.

Muscle power equal and normal: muscle tone good.

Spinal Sensory Nerves:

No impairment of sensation to pain or touch.

Muscle and tendon pressure sense normal.

position
Joint/sense normal.

Absence of vibration sense over ankles and patellae in both lower limbs.

Reflexes:

Abdominal reflexes present and normal.

Plantar reflexes: flexor.

Deep reflexes:	Upper limb:	Right	Left
	Biceps	+	+
	Brachio Radialis	+	+
	Triceps	+	+

Lower/

Lower Limb:	Right	Left
Knee-jerk	+	+
Ankle-jerk	+	+

Visceral Reflexes: There is perfect control of the bladder and rectum.
No trophic changes were detected.

Alimentary System.

Tongue: clean and moist.

Teeth: false.

Abdomen: Firm muscular wall. No tenderness or rigidity.
No fluid detected in the abdominal cavity.
Liver and spleen not palpated.

Skin and Subcutaneous Tissues.

There is extensive and widespread oedema.

In the feet and legs oedema extends up to the middle of the thighs. There is slight sacral oedema.
There is some swelling of the face round the eyes and there is marked subconjunctival oedema.

Locomotor System.

Nothing abnormal detected.

Endocrine System.

Nothing abnormal detected.

Blood.

27.1.49: Examination of the blood.-

Hb. 100%
White Blood Cell Count - 10,000 per cu. mm.
Blood Sedimentation Rate - 40 m.m./hour.

SPECIAL EXAMINATIONS.

Blood Biochemistry.

27.1.49.	Plasma Proteins - Albumen:	2.04 gm.%
	Globulin:	2.76 gm.%
	Non Protein Nitrogen:	61 mgm.%.
31.1.49.	Blood Urea Nitrogen:	50 mgm.%
11.2.49.	Blood Urea Nitrogen:	91 mgm.%
	Blood Sugar:	123 mgm.%

Oedema Fluid Biochemistry./

Oedema Fluid Biochemistry.

15.2.49.	Sugar:	606 mgm.%
	Chlorides:	600 mgm.%
	Total Protein:	0.40 gm.%
	Non Protein Nitrogen:	160 mgm.%
	Urea Nitrogen:	113 mgm.%

An estimation of the chloride content of the oedema fluid was made according to the method of Stewart and Dunlop (1949), and the fluid was found to contain more than 600 mgm.%.

Estimation of Urine Albumen.

The investigations were carried out on 24-hour specimens of urine by Esbach's method.

30.1.49	-	6 gm./litre
1.2.49	-	10 gm./litre
2.2.49	-	12 gm./litre
5.2.49	-	6 gm./litre
7.2.49	-	5 gm./litre
13.2.49	-	12 gm./litre
15.2.49	-	12 gm./litre
17.2.49	-	14 gm./litre
20.2.49	-	5 gm./litre
21.2.49	-	5 gm./litre
28.2.49	-	2.5 gm./litre
3.3.49	-	6.5 gm./litre

Estimation of Urinary Chlorides.

The investigations were carried out on 24-hour specimens of urine according to the directions of Stewart and Dunlop (1949).

4.2.49	-	less than 0.1 gm.%
8.2.49	-	less than 0.1 gm.%
12.2.49	-	less than 0.1 gm.%
16.2.49	-	0.1 - 0.3 gm.%
19.2.49	-	less than 0.1 gm.%
22.2.49	-	less than 0.1 gm.%
28.2.49	-	less than 0.1 gm.%
4.3.49	-	less than 0.1 gm.%

TREATMENT.

The type of treatment was dictated by the following considerations:-

- (1) The control of the diabetic condition.
- (2) Treatment of the nephritis and renal failure.
- (3) In the terminal stages, sedation of the patient.

The diabetes was controlled by giving the patient a special/

special diet and by the administration of insulin. The patient was given 200 gm.s of carbohydrate daily and he had a total daily intake of 2590 calories. The dosage of insulin was adjusted to the patient's needs by observing how much sugar was lost in the urine. The patient was stabilized by the administration of Zinc Protamine Insulin in the morning and soluble Insulin in the morning and evening. The doses varied considerably with the patient's general condition, and appetite. Owing to the fluctuations in the patient's condition and to his severe sickness and anorexia, some difficulty was experienced in controlling his diabetes, and several hypoglycemic reactions occurred which were controlled by oral and intravenous glucose. In the later stages his food intake was very low and it became difficult to obtain urine to test for sugar, and so his dosage of insulin was much reduced and, terminally, he did not receive any insulin.

The nephritic condition was treated by giving the patient a high protein and low salt diet which contained 90-120 gm. protein daily. He was also given potassium citrate, gr.10 Q.I.D., from 30.1.49 until 10.2.49. The latter was discontinued since the patient was distressed by it and he thought it was responsible for causing his sickness.

One Southey's tube was placed in each leg on 13.2.49, since the oedema had become very severe. The tubes drained successfully and 205 ounces of fluid were removed. The tube in the left leg was removed on 19.2.49 and that in the right leg on 21.2.49. As a result of this treatment, the oedema was greatly reduced all over the patient's body.

Vomiting and refusal of food were treated by administration of fluids and glucose. Until the last fortnight the administration was carried out orally, but on 22.2.49 an intravenous/

SUMMARY OF TREATMENT

1. Special diet administered containing:

Carbohydrate - 200 gm.

Protein - 90 - 120 gm.

Calories - 2510

Low salt

2. Dosage of Insulin

Date	Zinc Prot. Insulin	Soluble Insulin	
		a.m.	p.m.
27-30.1.49	32 units daily	10 units	20 units
13.2.-1.3:49	24-36 units daily	10 units	10 units
2.3.-6.3:49		10 units daily: on 7.3:49 and 8.3:49 the patient received no insulin.	

3. 30.1:49-10.2:49 Potassium Citrate gr. 10 Q.I.D.

4. Use of Southey's Tubes.

One tube was placed in each leg on 13.2.49

That in the left leg was removed on 19.2.49,

and that in the right leg on 21.2.49.

A total of 205 oz. of oedema fluid was
removed

5. An I.V. drip of 6% Glucose was given on 22-23.2.49 and 2000 cc. of fluid were administered.

6. Sedation:

11.2.49 Cyclobarbitone gr. 3.

13.2.49 Pethidine mgm. 200

14.2.49 A total of Heroin gr. $4\frac{3}{12}$
- 8.3:49 was given.

intravenous drip had to be started, and 2000 c.c. of 6% glucose were given. Following this, fluid and glucose were again given by mouth but the patient vomited nearly everything he took by mouth and his food and fluid intakes were very low until he died.

From 13.2.49 until he died on 2.3.49 constant and heavy sedation was necessary in order to keep the patient quiet and comfortable. This was carried out by injections of heroin, grain $\frac{1}{12}$, two or three times a day, before meals.

A summary of the treatment which was adopted is given in the table opposite.

PROGRESS.

The course of the disease was recorded by observations of.-

- (1) The degree of oedema as shown by measurements of the circumference of the legs, change in the patient's weight, and clinical examination of the chest and body. The circumference of the legs and thighs was measured each day at the same place:-

Leg measurement	-	4 inches below the tibial tuberosity.
Thigh	"	- 7 inches above the adductor tubercle.
- (2) The patient's mental and nervous state.
- (3) The patient's blood pressure, temperature, pulse and respiration rates.
- (4) Changes in the patient's general appearance and condition.

Measurements of the leg circumference, changes in weight and blood pressure readings are given in the table on the opposite page.

3.2.49. Examination of the Chest.

The bases of both lungs were stony dull on percussion. Vesicular breath sounds could be heard all over the lungs but vocal resonance was diminished at the right base. No accompaniments were heard.

Pitting oedema could be detected right up the lower limbs, over the sacrum and up to the level of/

SUMMARY OF PROGRESS

DATE	WEIGHT		B.P.	LEG MEASUREMENTS			
	STONE	LBS.		R. LEG	R. THIGH	L. LEG	L. THIGH
28:1	11	6	174/90				
29			174/94				
30	11	13					
31			170/70	13	$16\frac{1}{4}$	$13\frac{1}{4}$	16
1:2	12	$1\frac{1}{2}$					
2			178/96				
3	12	5					
5	12	3		13	$16\frac{5}{8}$	$13\frac{3}{8}$	$16\frac{5}{8}$
6			168/74				
7	13	0	168/92				
8			168/84	$13\frac{5}{8}$	$17\frac{1}{2}$	$13\frac{1}{4}$	$17\frac{1}{2}$
9	13	0	178/108				
10				13	$17\frac{7}{8}$	$13\frac{1}{4}$	$16\frac{1}{2}$
11	13	5					
12				$13\frac{7}{8}$	$18\frac{1}{8}$	$13\frac{1}{2}$	$17\frac{1}{4}$
13	13	9					
14			170/100				
15			170/100				
18:2			140/100				
5:3			138/70				

The temperature which had been normal until 24:2:49 did not exceed 97°F from that date until the patient's death.

The pulse rate which had been normal until 12:2:49 began slowly to rise after that date and varied between 80 and 110/minute until the patient's death.

The respiration rate became much depressed on 7:2:49 and remained low until the patient died.

Southey's tubes were put in the patient's legs on 13:2:49 and measurements of the circumference of his limbs were discontinued after that date.

of the posterior superior iliac spines.

No fluid was detected in the abdominal cavity.

The patient feels well but is troubled at night by a cough.

The patient looks well; his face is swollen, but his skin is healthy and elastic.

6.2.49. The patient had an insulin reaction this morning before breakfast, which was controlled by the intravenous administration of 10 gm. glucose followed by 20 gm. glucose by mouth.

7.2.49. Pitting oedema extends up to the rib margin posteriorly, and shifting dulness is present in the abdomen. The lung bases are dull on percussion and some crepitations can be heard over them. Subconjunctival oedema is still very severe.

The patient feels well, and, apart from the oedema, looks well.

8.2.49. The patient had another hypoglycemic reaction which was controlled by 5 gm. glucose given by mouth.

10.2.49. Pitting oedema extends up to the 5th thoracic spine and, on examination of the chest, breath sounds are indistinct, vocal resonance is diminished and many crepitations are present over the lower lobes.

The patient is much more ill than at any time since his admission. He is unable to sit up because of the extensive genital oedema and his appetite is poor. He has difficulty in starting to micturate and urine is constantly dribbling from him; its passage causes him discomfort and is painful. He was sick during the night and blames the potassium citrate for this. He was given 5 gm. glucose after he had been sick but immediately vomited again.

12.2.49. The patient is suffering from incontinence of urine. His general condition is still poor and is deteriorating. He is vomiting once or twice a day, particularly after food, and his appetite is poor.

16.2.49. Oedema is still present and severe, though the Southey's tubes are reducing it to some extent.

The patient is incontinent of urine, is nauseated, and vomits frequently. He is drowsy and sleeps much of the time. His face is grey and drawn. His breathing is stertorous.

18.2.49. The oedema is becoming less but the general condition of the patient is unchanged. A pustular eruption and purpuric rash has appeared over his chest and shoulders. He vomits any food or fluid/

fluid taken by mouth. Severe hiccough causes the patient periodic distress.

- 22.2.49. Treatment with the Southey's tubes has considerably reduced the oedema although crepitations can now be heard over the anterior wall of the chest when the patient is lying down. The patient is very drowsy and constantly vomiting; he is also very distressed and is becoming emaciated; incontinence of urine is still present and the patient hiccoughs occasionally. The patient is eating very little and it was decided that in spite of his oedematous condition intravenous glucose therapy was necessary. The glucose therapy resulted in a slight improvement in his condition but it was not maintained.
- 26.2.49. The patient is very emaciated but the oedema is starting to increase again. His sickness is less severe and the rash and pustular eruption is fading. He still hiccoughs occasionally and is incontinent of urine.
- 4.3.49. The patient's general condition is deteriorating. He is still vomiting and has a very poor appetite. He is drowsy and exhausted. His eyes are sunken, his lips are dry and he complains of thirst. His pulse is very faint and running. The rash and pustular eruption have disappeared.
- 7.3.49. Respiration became depressed in the evening and loud hiccough occurred. The patient has been taking no food for the last two days. He is tired and exhausted and is semi-conscious most of the time. Urinary incontinence has become extreme.
- 8.3.49. The patient died early in the morning. From 4.3.49 until his death the patient had had no bowel movement.
Post-mortem examination was refused.

DISCUSSION.

The uneventful diabetic history of this patient, with the sudden onset of features suggestive of renal disease and his rapid progress into uraemic coma and death, provide a puzzling pathological picture. The discussion of this case must resolve itself into an attempt to establish a diagnosis of the acute condition; to trace the pathological course of the condition in view of the clinical and biochemical findings, and to decide why such an acute condition ever arose. Treatment could only be symptomatic, and so it is only by a consideration of the pathological changes in such a case that any hope of prophylaxis may be envisaged for the future.

Diagnosis, Pathology and Progress.

In the absence of a post-mortem, the exact nature of this condition cannot be diagnosed. Only by a comparison of the clinical features of this case with other reported cases can any conclusion be drawn as to the probable pathological condition.

Gauld et al. have reported a series of cases in which renal symptoms and signs complicated diabetes. The features of this patient closely resemble those of a patient whom they describe, with symptoms and signs of subacute nephritis during the course of diabetes.

In the patient reported here there is a long history of diabetes which has been well controlled and during which there have been no indications of any renal changes taking place until shortly before the patient was admitted. This does not prove that no changes had occurred but only that no changes had occurred of such severity as to produce signs and symptoms of early renal failure. The history, albuminuria, and elevation of the blood urea nitrogen all indicate that renal pathology is present and that the oedema is of renal origin.

The origin of the renal pathology which was present at the time of admission must be discussed.

1. Cardio-vascular origin. To produce a degree of damage sufficient to cause such severe clinical features and to produce death from uraemic coma seven weeks after the onset of the illness, either (a) a very malignant form of hypertension would have to be present, or (b) a fairly advanced degree of vascular disease which, because of the coryza, underwent an exacerbation so that death occurred as a result of chronic hypertension which terminally became exaggerated. Had malignant hypertension been present, the blood pressure would have been at a much higher level and symptoms and signs of encephalopathy would probably have occurred. If a benign form had been present, retinal vascular changes would have been observed and there would have been some enlargement of the heart. Thus it seems most unlikely that vascular changes in the kidney could have accounted for renal damage.

2. Local Renal Origin. The presence of a history of acute glomerulo-nephritis is not essential before making a diagnosis of subacute glomerulo-nephritis in a patient who presents the clinical features of the latter condition. In nephrosis similar clinical features are present and the differential diagnosis between these two conditions appears to depend on the degree and histological appearance of the tubular damage found post-mortem. In the nephrosis it is believed that the principal damage is in the tubules, with relatively little damage to the glomeruli, while in the glomerulo-nephritis glomerular damage may be fairly severe. Beattie and Dickson state that nitrogen retention occurs in neither condition but this probably only applies to the earlier stages since some elevation is to be expected as the conditions proceed to chronic/

chronic glomerulo-nephritis. The fact that this patient shows nitrogen retention suggests that the early stage is past and that the stage of chronic glomerulo-nephritis is approaching. The albuminuria, oedema, low plasma proteins and chloride retention are all characteristic of subacute nephritis. The blood pressure may or may not be raised in this condition but does not reach the high value found in chronic nephritis. The high specific gravity of the urine is accounted for by the glycosuria and albuminuria.

In Kimmelstiel-Wilson's disease a characteristic hyalinization of inter-capillary connective tissue is found in the kidney post-mortem, and the clinical features of oedema and renal failure, together with diabetes, are present during life. There is some doubt whether this pathological lesion is of prime aetiological significance in the pathology of renal failure and it is possible that associated vascular changes account for the renal damage.

In the case which Gauld et al describe, in which a post-mortem was performed, no Kimmelstiel-Wilson lesions were discovered, but only the pathological lesions of sub-acute nephritis. This case, and two other cases which these workers describe, bear a striking clinical resemblance to that of James Lowe. The absence of retinal changes, the relatively low blood pressure and acute course of the disease are all of significance and would suggest that vascular changes were probably not extensive in any of these cases. Gauld et al. have found Kimmelstiel-Wilson lesions in many of their patients and are of the opinion that they are not responsible for the clinical features but that associated vascular disease is. However, in their patients who had vascular disease the clinical features of it could generally be recognised during life. The fact that/

that a patient does not show features of vascular disease does not mean that he did not have Kimmelstiel-Wilson disease and in a patient like James Lowe it would seem almost essential that some factor was present which produced the rapid deterioration in the absence of gross signs of vascular disease, and in such patients the diabetes is naturally blamed.

In conclusion it may be stated that this patient showed the features of subacute nephritis in the absence of vascular disease; that the subacute nephritis was accompanied by signs that showed that the patient was progressing rapidly towards Type III nephritis, and that death occurred unusually soon after the onset of symptoms of subacute nephritis, the only predisposing feature for which appeared to be the long diabetic history.

Treatment and Progress.

Until the onset of symptoms, treatment consisted of a strict control of the diabetes. The renal failure could not be anticipated and even if it had been little could have been done to prevent it. When it did occur, treatment was only symptomatic. The administration of a high protein diet in order to try to increase the plasma proteins by replacement therapy did not have a beneficial effect as judged by the persistence and increase of the oedema. The classical teaching is that the oedema is the result of the low osmotic pressure of the blood which occurs because of the loss of plasma proteins in the urine. Some doubt has been cast on this theory by recent French investigations, as a result of which it is concluded that in hunger oedema loss of osmotic pressure is much greater than can be accounted for by the fall in protein content. It is assumed that this is due to some of the small-molecule protein being substituted by large-molecule/

molecule protein; it is also suggested that other factors, probably of a vascular nature, are involved (Barnes, 1948). Treatment of the condition by a high protein diet is the only method of therapy known; its effect was insufficient in this case to improve the oedema, probably because attempts at replacement therapy by giving a high protein diet were not sufficiently specific to rectify the underlying disturbance of physiological function which the French work indicates may be present in conditions where oedema is associated with low plasma protein levels.

The remaining treatment consisted of insulin therapy and salt restriction in an attempt to limit the spread of oedema by reducing the sodium ion intake which is believed to be responsible for maintaining the osmotic pressure of the oedema fluid. That conservation of salt occurs in the presence of oedema is shown by the marked reduction of salt excretion in the urine throughout the illness. A large proportion of the salt which is thus retained must be held in the oedema fluid, as shown by its high salt content.

Treatment in the terminal stages consisted of sedation and the mechanical removal of fluid. Uraemia had appeared, the prognosis became hopeless. The rapid progress of the disease during the last month must have resulted from a deterioration in the patient's general metabolic processes. The vascular disease with which Gauld et al. explain the pathology of the condition cannot have accounted for this rapid failure in the presence of only a mild hypertension. The disturbance of metabolism may have been linked with the patient's diabetic condition, but it is probable that some further deficiency or physiological dysfunction was superimposed upon it.

SUMMARY

In the discussions of the cases emphasis has been laid on the diagnosis of the conditions which in the early stages of the disease were definite, but which particularly in cases III, IV and V have been complicated by subsequent pathological changes. An attempt has been made to trace the progress of these pathological changes particularly with a view to discovering their relation to the initial condition and their possible aetiology. In case I a complex malabsorption syndrome is present, the possible origin of the clinical features which were exhibited is discussed and the basis and efficacy of their treatment is considered with particular reference to the prospect of cure and ultimate prognosis. In case II a general endocrine disturbance was present, when this was realised and suitable treatment was instituted clinical features not commonly associated with the menopause or with thyrotoxicosis alone were relieved and a general improvement in health occurred.

In case I diagnosis of a complicated glandular condition was made and treatment of each of the endocrine disorders was carried out. This combined treatment was more effective than treatment of the thyrotoxicosis alone and the prognosis was correspondingly improved. Treatment of the diabetes at the menopause with oestrogens (Lancet 1948 II 659) has been described and in this condition also treatment may be effective presumably because the pathological endocrinology is similar to that in case I.

In case II disturbance of absorption is probably the main pathological lesion. By suitable dietetic therapy the clinical features can be improved and by the use of folic acid the condition of the blood can be improved more rapidly and probably more completely than is possible by dietetic means alone. However though improvement can thus be brought

brought about the treatment is not of a sufficiently specific nature to cure the malabsorption and until this is done substitution therapy with folic acid and a high protein mineral and vitamin diet will be necessary. In spite of such continued therapy experience of this condition shows that complications may ultimately be expected in the form of osteoporosis and symptoms due to chronic deficiency of other factors.

In cases III IV and V the complications can possibly be attributed to a continued disturbance of carbohydrate metabolism. Pathological studies suggest that in each of these cases initial disease of the vascular system may have led subsequently to disease in the renal or nervous system. Why in one case the nervous system and in the others the renal systems particularly should have shown signs of disease cannot be determined, in case III it may have been because there was some congenital weakness already present in the vessels of the nervous system. In cases III and IV there is little evidence that the connection between the vascular and endocrine disease is anything but fortuitous although in case IV the permanent renal damage in the absence of the history of of any other predisposing condition might be attributed to the diabetes. In case V however, by elimination, there seems to be no reason why the rapid renal failure should have occurred except as a result of the diabetes. Gauld et al. state that the renal lesions in diabetes do not cause any of the clinical features of nephritis, this may be so but it does not mean that diabetes cannot predispose to the occurrence of the vascular lesions in the kidneys to which they attribute the kidney failure. Croom and Scott are definitely of the opinion that in diabetic patients there is present a factor which predisposes to vascular disease. The findings in these cases supports this view. Until the reason for the production

production of such a factor is discovered, until it is discovered why the factor is present in some people and not in others, and until the control of the factor by therapy is secured, the ultimate prognosis in diabetes must be guarded. Treatment of diabetes by insulin has eliminated the immediate mortality of the disease, if the treatment is strict and maintained the ultimate prognosis is probably favourable, but until more thorough investigation of the metabolic changes which take place during the control of the disease are made with particular reference to the relation between vascular disease and the patient's metabolism the prognosis must remain guarded.

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